201-14624

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August 27, 2003

Christie Todd Whitman, Administrator
US EPA
P.O. Box 1473
Merrifield, VA 22116
Attn: Chemical Right-to-Know Program

Dear Ms. Whitman:

On behalf of Eastman Chemical Company, I am pleased to submit the Test Plan and Robust Summaries for the substance designated as "Methyl 4-formylbenzoate" to the HPV Challenge Program, AR-201. We are submitting the test plan and accompanying robust summaries directly to EPA to make available to the public. This submission includes one electronic copy in pdf. format. A hard copy of this submission is available upon request. The EPA registration number for Eastman Chemical Company is

Please feel free to contact me with any questions or comments you might have concerning the submission at tadams@therobertsgroup.net, tadams@chemintox.com or 202-331-2325.

Sincerely,
Timothy Adams, Ph.D.
Technical Contact Person for Eastman Chemical Company

Test Plan for Methyl 4-formylbenzoate

Methyl 4-formylbenzoate

CAS No. 001571-08-0

Eastman Chemical Company

Submitted to the EPA under the HPV Challenge Program by:
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The High Production Volume Challenge (HPVC) Program

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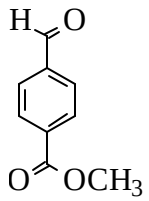
1 IDENTITY OF SUBSTANCES



Methyl 4-formylbenzoate

CAS NO. 001571-08-0

Synonyms:

4-formyl benzoic acid, methyl ester
terephthalaldehydic acid, methyl ester
methyl terephthaldehydate
p-formylbenzoic acid, methyl ester
4-(methoxycarbonyl) benzaldehyde
4-carbomethoxybenzaldehyde
methylbenzaldehyde-4-carboxylate
4-carboxybenzaldehyde, methyl ester
p-carbomethoxybenzaldehyde

2 CHEMICAL ANALYSIS

2.1 INTRODUCTION

In November of 1999, Eastman Chemical Company (Eastman) committed to participate in the Chemical "Right-to-Know" Program. As part of this commitment, Eastman is committed to assembling and reviewing available test data, developing and providing test plans for methyl 4-formylbenzoate, and, where needed, conducting additional testing. The test plan and robust summaries presented are the first phase of Eastman's commitment to the Chemical "Right-to-Know" Program.

2.2 BACKGROUND INFORMATION

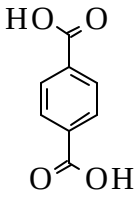
Methyl 4-formybenzoate is a by-product in the manufacture of dimethyl terephthalate. Methyl 4-formybenzoate is separated from the dimethyl terephthalate by distillation. The composition of the isolated methyl 4-formylbenzoate is greater than 90%. Other minor secondary components include less than 3% dimethyl terephthalate, less than 2% methyl 4-carboxybenzoate, less than 2% methyl 4-methylbenzoic acid, and smaller amounts of benzoic acid and 4-methylbenzoic acid.

As a by-product in the preparation of dimethyl terephthalate, methyl 4-formybenzoate has limited commercial use. It is mixed with a number of other chemicals to make blends used in sand castings. The blend material is completely oxidized either in the casting process or in the treatment of the sand. The castings are used predominantly in the USA automotive market. With its only use being in industrial applications there is minimal opportunity for exposure to the general public and exposures in the workplace are minimized through appropriate industrial hygiene practices.

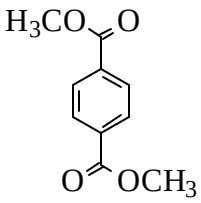
2.3 STRUCTURAL CLASSIFICATION

Methyl 4-formylbenzoate is a benzene derivative ring-substituted with a methyl ester and an aldehyde functional group. The functional groups are situated on the 1- and 4-position of the aromatic nucleus. The mono-substituted aromatic substances methyl benzoate and

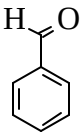
benzaldehyde each contain one of the two functional groups present in methyl 4-formylbenzoate. Given that the aldehyde function is oxidized to a carboxylic acid (see Section 2.4.2) and that the methyl ester is hydrolyzed to yield the corresponding carboxylic acid (see Section 2.4.1), methyl 4-formybenzoate readily forms the diacid terephthalic acid (*i.e.*, 1,4-benzenedicarboxylic acid; terephthalic acid) in nature and as a metabolite in animals. This test plan includes data for methyl 4-formylbenzoate and several related benzyl derivatives including benzaldehyde, methyl benzoate, sodium benzoate, benzoic acid, terephthalic acid, and dimethyl terephthalate, the latter, like methyl 4-formylbenzoate, also hydrolyzes to terephthalic acid. As stable animal metabolites, benzoic acid and 1,4-benzenedicarboxylic acid are excreted primarily in the urine either free or conjugated with glycine. These reaction pathways have been reported in both aquatic and terrestrial species. Based on the polarity of product formed by ester hydrolysis and aldehyde oxidation (*i.e.*, terephthalic acid), it is concluded that the metabolite is rapidly eliminated and, therefore, exhibits low toxicologic potential.



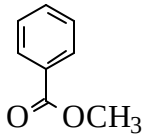
terephthalic acid



dimethyl terephthalate



benzaldehyde



methyl benzoate

The data summarized in the test plan and data recorded in the robust summaries for structurally related substances have been previously submitted to the Office of Economic and Community Development (OECD) and the U.S. Environmental Protection Agency (EPA). Data for terephthalic acid and dimethyl terephthalate were submitted in the form of Safety Information Data Sheets (SIDS) to the OECD by the EPA. The test plans and robust summaries were accepted with no requests for additional testing. Robust summaries used in the preparation of these SIDS submissions have been included in this document.

In addition, the Flavor and Fragrance High Production Volume Consortia (FFHPVC) has submitted (12/01) a test plan and robust summaries for the chemical category named "Benzyl Derivatives" including data for ten benzyl derivatives. EPA commented (12/02) on this test plan and robust summaries. The robust summaries for methyl benzoate, benzaldehyde, benzoic acid and sodium benzoate for which no revisions or additional information were requested or ones in which requested information has been added are also included in this document.

2.4 CHEMICAL REACTIVITY AND METABOLISM

2.4.1 Hydrolysis of Esters

The hydrolysis of benzoate esters occurs in the environment and in animals. Uncatalyzed hydrolysis of methyl 4-formybenzoate occurs readily at a slightly basic pH=9. Greater than 50% hydrolysis to yield 4-formylbenzoic acid was observed after 2.4 hours at pH=9, indicating the half-life of the ester is less than 1 day. The estimated half-life at pH=7 is estimated to be approximately 200 days [Hoffman, 2003]. The rates of enzyme-catalyzed hydrolysis reported for benzoate esters in animals are orders of magnitude greater than uncatalyzed rates mentioned above.

In general, the catalytic activity of carboxylesterases or esterases such as the *beta*-esterases hydrolyzes aromatic esters *in vivo* [Heymann, 1980]. These enzymes are found throughout mammalian tissues, but predominately in hepatocytes [Anders, 1989; Heymann, 1980]. The hydrolysis of benzoate esters yields the corresponding benzoic acid derivatives in several *in vitro* experiments.

In a series of hydrolysis experiments with 4 alkyl benzoates (including methyl benzoate) and 2 aryl benzoates, plasma half-lives ($t_{1/2}$) in 80% human blood plasma decreased from 210 minutes for ethyl benzoate to 24 minutes for butyl benzoate and 19 and 15 minutes for phenyl benzoate and benzyl benzoate, respectively [Nielson and Bundgaard, 1987].

Experiments *in vivo* confirm rapid hydrolysis of benzoate esters in animals. Methyl 2-hydroxybenzoate was orally administered to males rats at a dose equivalent to 500 mg/kg

bw of 2-hydroxybenzoic acid [Davison *et al*., 1961]. Twenty minutes following dosing, plasma levels showed complete hydrolysis of methyl 2-hydroxy benzoate. Similarly, male dogs were given 320 mg/kg bw of the methyl ester in capsules. After one hour, blood samples showed 95% hydrolysis of methyl ester to 2-hydroxybenzoic acid. In humans given 0.42 ml methyl 2-hydroxybenzoate (approximately 500 mg), blood samples showed 79% of the dose hydrolyzed within the first 90 minutes.

Several experiments were conducted [Jones *et al*., 1956] to study the hydrolysis of *p*-hydroxybenzoic acid esters. Comparisons were made between oral (1,000 mg/kg bw) and intravenous (50 mg/kg bw) administration in dogs. Methyl and ethyl esters were rapidly hydrolyzed by esterases in the liver and kidney. Recovery of the dose of butyl *p*-hydroxybenzoate was 48% and 40% from the oral and intravenous administration, respectively. Liver preparations from dogs injected with 100 mg/kg bw of the methyl, ethyl, or propyl benzoate showed 100% hydrolysis in 3 minutes; whereas, 100% hydrolysis of the butyl ester occurred after 30-60 minutes.

Carboxylesterase (Type B) activity has been reported in a variety of fish species at different life stages [Leinweber, 1987; Boone and Chambers, 1996; Abas and Hayton, 1997; Barron *et al*., 1999]. Enzyme activity of rainbow trout sera, liver and whole body homogenates were similar to those of rat liver homogenate. A significant increase (300%) in activity occurred between yolk-sac and juvenile stage of rainbow trout development. Carboxylesterase activity was not significantly different for whole body homogenates of the rainbow trout, channel catfish, fathead minnows, and bluegill [Barron *et al.*, 1999]. These data support the conclusion that simple aromatic benzoate esters are readily hydrolyzed in these animals.

In summary, the methyl 4-formylbenzoate is expected to hydrolyze to the corresponding benzoic acid derivative, 4-formylebnzoic acid, *in vivo*. Complete hydrolysis is expected to occur in gastric juice, intestinal fluid, portal blood and liver. Slower hydrolysis is expected in uncatalyzed environments.

2.4.2 Oxidation of the Aldehyde in Methyl 4-formybenzoic Acid

The aldehyde functional group in methyl 4-formylbenzoic acid is expected to be readily oxidized by aldehyde dehydrogenase (ALD) to the corresponding benzoic acid derivative. Based on the data that the ester function of methyl 4-formylbenzoate is hydrolyzed prior to absorption, the rapid oxidation of the aldehyde (formyl) function would then yield 1,4-benzenedicarboxylic acid (terephthalic acid) as the principal metabolite of methyl 4-formylbenzoate. Based on the metabolism of related aromatic esters (*i.e.,* benzyl acetate), hydrolysis and oxidation to the benzoic acid derivative is extremely rapid *in vivo.*

When benzyl acetate was fed or administered by gavage to rats, no benzyl acetate, benzyl alcohol or benzaldehyde was observed in the plasma. However, high plasma levels of hippuric acid (glycine conjugate of benzoic acid) and unconjugated benzoic acid were detected indicating that benzyl acetate is rapidly hydrolyzed to benzyl alcohol, which is then rapidly oxidized first to benzaldehyde and then to benzoic acid [Yuan *et al.,* 1995].

Groups of male F344 rats and B6C3F1 mice were administered [^{14}C]-benzyl acetate orally at levels up to 500 and 1,000 mg/kg bw, respectively, 5 days/week for a period of two weeks [Abdo *et al*., 1985]. The ester was readily absorbed from the gastrointestinal tract of both species and approximately 90% and 0.3-1.3% of the total dose was recovered as hippuric acid in the urine and feces, respectively, within 24 hours. No benzyl acetate-derived radioactivity was detected in any tissue (i.e., blood, liver, muscle, adipose, skin, lung, kidney and stomach) analyzed at 24 hours. The clearance pattern was not affected at any dose tested. Such complete clearance indicates that aromatic esters are readily absorbed, hydrolyzed to component acids and alcohols, which in turn are oxidized to the corresponding aromatic acids, and excreted.

The rapid conversion to the benzoic acid derivative has also been documented at high dose levels in rats. [^{14}C]-Benzyl acetate administered by gavage to groups of male F344 rats at doses of 5, 250, or 500 mg/kg bw as the substance alone, in corn oil, or propylene glycol, resulted in excretion of 70-89% of the dose in the urine within 24 hours [Chidgey and Caldwell, 1986]. Only about 4% of the radioactivity was detected in the feces after

72 hours. Independent of the vehicle, the elimination of benzyl acetate and metabolites, was essentially complete after 3 days. No benzyl acetate was detected in the plasma or urine; however, minute amounts of benzyl alcohol were detected in the plasma. At the highest dose, benzoic acid was by far the major plasma metabolite, while at the lowest dose, conjugated benzoic acid (hippuric acid) was the major urinary metabolite. Of the metabolites, the proportion of the benzoic acid glucuronic acid conjugate increased with increasing dose, while low levels (1.0-3.6%) of free benzoic acid and benzylmercapturic acid were not affected by dose or vehicle.

To determine the effects of age on disposition of benzyl acetate, 3 to 4-, 9-, and 25-month-old F344 rats and 2-, 13-, and 25-month-old C57BI/6N mice were given a single oral dose of [^{14}C]-benzyl acetate at doses of 5 or 500 mg/kg bw (rats) or 10 mg/kg bw (mice) [McMahon *et al*., 1989]. In rats, approximately 80% of radioactivity was recovered in the urine in the first 24 hours for all age groups. The major urinary metabolite was hippuric acid (percentage excreted was not affected by age) and a minor urinary metabolite was benzylmercapturic acid (percentage excreted was slightly increased in 25-month-old rats). The percentage of radioactivity excreted in the feces was slightly decreased in the 25-month-old group. In mice, hippuric acid was the major urinary metabolite (93-96% of the total dose, with lower percentages excreted in 25-month-old mice than in the younger groups). Fecal excretion was a minor route of elimination and was independent of age. The authors concluded that formation of hippuric acid is not affected by age, but aging does affect the minor routes of metabolism and excretion of benzyl acetate in rats and mice.

F344 rats and B6C3F1 mice were used to study the effect of gavage versus dietary administration on the toxicokinetics of benzyl acetate [Yuan *et al*., 1995]. Groups of F344 rats were given a single dose of 500 mg/kg bw of benzyl acetate by gavage in corn oil or were fed diets containing 2,700 ppm (approximately 648 mg/kg bw/d) benzyl acetate for 7 days. Similarly, groups of B6C3F1 mice were given benzyl acetate, 1,000 mg/kg bw by gavage in corn oil or were fed diets containing 10,800 ppm benzyl acetate (approximately 900 mg/kg bw/d) for 7 days. Plasma levels of benzyl alcohol, benzoic acid and hippuric acid were measured at 24-hour intervals. Benzyl acetate was

undetectable in the plasma after gavage (after 5 minutes in mice and 10 minutes in rats) or dietary administration. Peak plasma levels of benzoic acid and hippuric acid were reached within 3 hours of gavage administration. Compared to the gavage mode of administration, peak plasma concentrations of benzoic acid were 40-fold less in rats and 300-fold less in mice after dietary administration. Plasma concentrations of hippuric acid were similar regardless of the mode of administration. Based on the above studies it is apparent that ester hydrolysis and functional group oxidation occurs rapidly *in vivo* and is independent of dose, species, age, and mode of administration. Other studies also support the rapid *in vivo* oxidation of the benzaldehyde functional group.

Oxidation of the benzaldehyde moiety by aldehyde dehydrogenase (ALD) has been reported to yield the glycine conjugate of benzoic acid [Bray *et al*., 1951; NTP, 1990]. In the rabbit, approximately 83 % of single doses of 350 or 750 mg/kg bw of benzaldehyde is excreted in the urine of both dose groups.

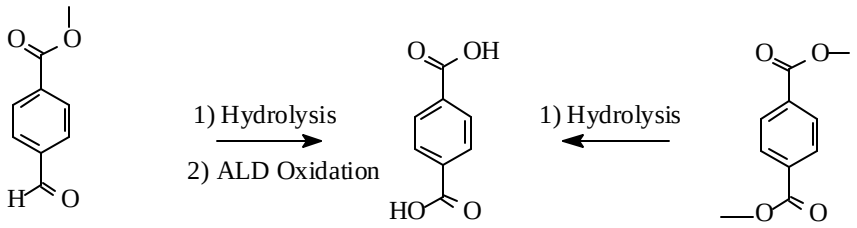
In male albino rats, approximately 100% of a 100 mg/kg bw dose of 4-hydroxy-3-methoxybenzaldehyde in a propylene glycol/water solution was excreted as free or conjugated benzoic acid derivatives in the urine within 24 hours [Strand and Scheline, 1975]. Sprague-Dawley albino rats were given 100 mg/kg bw of 4-hydroxy-3-methoxybenzaldehyde in 0.9% NaCl by intraperitoneal injection. Sixty percent of the dose was recovered in the 24-hour urine mainly as unconjugated 4-hydroxy-3-methoxybenzoic acid and the sulfate and glucuronic acid conjugates. Minor amounts of the conjugates of 4-hydroxy-3-methoxybenzaldehyde, 4-hydroxy-3-methoxybenzyl alcohol, and catechol were also detected [Wong and Sourkes, 1966]. Free and conjugated forms of 4-hydroxy-3-methoxybenzoic acid identified in the urine represented greater than 80% of the dose.

Female albino rats injected intraperitoneally with 52.4 mg of 2,4-dihydroxybenzaldehyde excreted approximately 6% of the dose in the urine as the corresponding hippurate within 24 hours [Teuchy *et al*., 1971].

Based on data for ester hydrolysis and aldehyde oxidation, methyl 4-formylbenzoate is expected to be rapidly hydrolyzed to yield 4-formylbenzoic acid that is then rapidly

oxidized (see Figure 1) to yield 1,4-benzenedicarboxylic acid (terephthalic acid). Based on pharmacokinetic evidence discussed above terephthalic acid is the predominant *in vivo* metabolite.

Figure 1



Methyl p-formylbenzoate

1,4-Benzenedicarboxylic acid (terephthalic acid)

Dimethyl 1,4-benzenedicarboxylate (dimethyl terephthalate)

2.4.3 Absorption, Distribution, Metabolism, and Excretion

Following hydrolysis of methyl 4-formylbenzoate in the gastrointestinal tract, the corresponding benzoic acid derivative, 4-formylbenzoic acid is rapidly absorbed and oxidized primarily in the liver to terephthalic acid. Terephthalic acid is then excreted in the urine either unchanged or conjugated. Data on structurally related benzoic acid derivatives support this conclusion [Jones *et al*., 1956; Davison, 1971; Abdo *et al*., 1985; Temellini *et al*., 1993].

Absorption, distribution, metabolism, and excretion studies have been conducted with various benzyl derivatives. The most relevant of these is the *in vivo* metabolite of methyl 4-formylbenzoate, terephthalic acid, and dimethyl terephthalate, a precursor of terephthalic acid. Other benzyl derivatives containing benzaldehyde and benzoate ester provide additional data on the pharmacokinetic potential and metabolic fate of methyl 4-formylbenzoate (*m*-methoxy-*p*-hydroxybenzaldehyde, benzoic acid, benzyl alcohol, 4-hydroxybenzyaldehyde, 4-hydroxybenzoic acid, 2-hydroxybenzoic acid, 2,4-dihydroxybenzyaldehyde, butyl *p*-hydroxybenzoate, 3,4-dimethoxybenzaldehyde,

sodium benzoate, and 2-hydoxybenzaldehyde). These substances exhibit remarkably similar patterns of pharmacokinetics and metabolism.

2.4.3.1 Rats and Mice

In female Wistar rats given a single gavage dose of 85 mg/kg bw of terephthalic acid, expired air and feces collected over 24 hours accounted for less than 0.04 and 3.3% of the total radioactivity administered, respectively [Hoshi and Kuretani, 1967]. Most of the dose was excreted in the urine within 24 hours and no other urinary metabolites were detected. The authors determined that approximately 70 and 26% of the dose was absorbed through the upper and lower gastrointestinal tract, respectively. In a separate study, female rats undergoing the same treatment were killed and blood and tissue samples were assayed for radioactivity [Hoshi and Kuretani, 1968]. After 6 hours, radioactivity was detected in plasma, kidney, liver, brain, skin, lung, pancreas, spleen, fat, heart, muscle, bone, erythrocytes, uterus, ovary, and endocrine glands. The highest concentrations were detected as follows: kidney greater than liver greater than plasma. After 48 hours, no radioactivity in these tissues was detected. A half-life of 1.2-3.3 hours was determined for terephthalic acid with first-order kinetics elimination. Oral exposure to terephthalic acid results in wide bodily distribution, but no accumulation.

The excretion of terephthalic acid following various routes of administration (gavage, intraperitoneal injection, and feeding) were studied in male rats [Hoshi and Kuretani, 1965]. Twenty-four hours following a gavage dose of 200 mg/kg bw of terephthalic acid, unchanged terephthalic acid was detected in the urine (55% of the dose) and feces (30% of the dose). After an intraperitoneal injection of 200 mg/kg bw of terephthalic acid, most of the dose was recovered in the urine within 24 hours. Feeding 300 mg/kg bw of terephthalic acid to rats resulted in excretion of 78-85% of the dose in urine and the remainder in the feces after 24 hours.

Over a period of 25 days, rats were exposed by inhalation to a particulate aerosol of 10 mg/cubic meters terephthalic acid for 6 hours/day [Amoco Corporation, 1989a]. Blood concentrations of terephthalic acid were detectable only after 10 days of exposure with progressively increasing blood levels to exposure termination reaching a high of 2.7

micrograms/ml after 25 days. After a 7-day recovery period, blood levels were less than 1 micrograms/ml.

Studies on and ester precursor of terephthalic acid, dimethyl terephthalate, indicate that the ester is hydrolyzed and the resulting acid is rapidly excreted as terephthalic acid.

Groups of rats and mice were given a single oral dose of C^{14}-dimethyl terephthalate (amount not specified) and urine and feces were collected over a 48-hour period [Heck, 1980]. Using reverse-phase HPLC, terephthalic acid was the only urinary metabolite identified in rats; whereas, in mice, the urinary metabolites identified consisted of monomethyl terephthalate (70%), terephthalic acid (30%) and traces of unchanged dimethyl terephthalate. Similar metabolites were identified in the feces. Dimethyl terephthalate did not lower the concentration of nonprotein sulfdryl groups, leading the authors to conclude that dimethyl terephthalate is not activated to form electrophilic metabolites.

In another oral study, rats were administered either a single dose or 5 oral doses (1 dose every other day over 10 days) of 0, 20, or 40 mg labeled dimethyl terephthalate [Moffitt *et al*., 1975]. More than 83% of the single dose of labeled dimethyl terephthalate was excreted within 48 hours, with 86% and less than 10% of the radioactivity identified in the urine and feces at 48 hours, respectively. Following repeat dosing, greater than 91% of the total dose was identified in urine and feces within 24 hours after the final dose.

Groups of rats and mice were given a single oral dose of C^{14}-dimethyl terephthalate (amount not specified) and urine and feces were collected over a 48-hour period [Heck, 1980]. Ninety and 10% of the dose was excreted in the urine and feces, respectively, in both species. Less than 1% remained in the animal carcasses after 48 hours.

Other benzaldehyde derivatives have also been shown to undergo rapid oxidation and excretion as the benzoic acid derivative. Male albino rats were administered the benzaldehyde derivative 4-hydroxy-3-methoxybenzaldehyde, 100 mg/kg bw in a solution of propylene glycol and water by stomach tube [Strand and Scheline, 1975]. Only trace amounts of benzoic acid derivatives remained in the urine after the first 24 hours and

none after 48 hours. Free and conjugated forms of 4-hydroxy-3-methoxybenzoic acid were the predominant metabolite excreted in the urine within 24 hours.

Sixty percent (60%) of a 100 mg/kg bw dose of 4-hydroxy-3-methoxybenzaldehyde given to Sprague-Dawley albino rats by intraperitoneal injection was recovered in the 24-hour urine mainly as unconjugated 4-hydroxy-3-methoxybenzoic acid and the sulfate and glucuronic acid conjugates of the acid conjugates [Wong and Sourkes, 1966].

Following administration of 375 mg/kg bw orally to rats or by intraperitoneal injection to mice of [^{14}C]-benzoic acid, 88-89% of the radioactivity was recovered in the urine within 24 hours and 91-94% after 72 hours [Nutley, 1990]. Only 1-6% was present in the feces.

Female albino rats injected intraperitoneally with 52.4 mg 2,4-dihydroxybenzaldehyde excreted approximately 6% of the dose in the urine as the corresponding hippurate within 24 hours [Teuchy *et al.,* 1971].

2.4.3.2 Rabbits

Rabbits fed 1,000 mg /kg bw of 4-hydroxy-3-methoxybenzaldehyde by gavage, excreted in the urine, 69% of the dose as free and conjugated 4-hydroxy-3-methoxybenzoic acid [Sammons and Williams, 1941].

Rabbits were administered 200 mg of 3,4-dimethoxybenzaldehyde by stomach tube [Sammons and Williams, 1941]. Within 24 hours, approximately 70% of the dose was recovered in the urine as free corresponding acid (approximately 28%) and its glucuronic acid (approximately 38%) or sulfate (3-7%) conjugate.

In the rabbit, single doses of 350 or 750 mg/kg bw of benzaldehyde were excreted in the urine (approximately 83 %) by oxidation to benzoic acid and then excretion predominantly as hippuric acid (approximately 68%) [Laham *et al.,* 1988]. Other urinary metabolites identified were benzoyl glucuronic acid (10%), benzoyl glucuronide (3%), and free benzoic acid (1.5%).

2.4.3.3 Dogs

Groups of fasted dogs were orally administered 1,000 mg/kg bw of butyl *p*-hydroxybenzoate, or intravenously injected with 50 mg/kg bw of butyl *p*-hydroxybenzoate [Jones *et al*., 1956]. Blood and urine samples were collected at fixed intervals until the levels returned to background levels within 48 hours. Most of the dose was recovered between 6 and 30 hours after dosing as the *p*-hydroxybenzoic acid conjugate of glucuronic acid at 48% and 40% for the oral and intravenous route, respectively. Although the relatively low rate of recovery seen in both dosing methods was attributed to incomplete hydrolysis of the ester in the body, *in vitro* incubation of the butyl ester with freshly prepared liver homogenate showed complete hydrolysis within 30-60 minutes. Studies conducted with other related benzoate esters, such as methyl and ethyl *p*-hydroxybenzoate, showed significantly higher rates of material recovery suggesting that an increase in the homologous series of alkyl esters may result in the activation of other metabolic and excretion pathways. Overall, the authors concluded that butyl *p*-hydroxybenzoate and other alkyl esters are readily absorbed, metabolized, and excreted by the body.

2.4.3.4 Humans

In humans, 4 full-term and 9 pre-term infants were administered intravenous or intramuscular doses of 0.007-0.222 mmol/kg bw of benzyl alcohol in medication [LeBel *et al*., 1988]. Pre-term infants had maximum serum concentration levels of benzoic acid approximately 10 times those in full-term infants. Benzoic acid was found at higher percentages in the plasma than hippuric acid regardless of administration route in pre-term infants compared to term infants indicating that glycine conjugation is deficient in pre-term compared to full-term infants.

In humans receiving oral doses of 40, 80, and 160 mg/kg bw of sodium benzoate, the clearance of benzoic acid increased disproportionately to dose while the clearance for hippuric acid was proportional to dose [Kubota *et al*., 1988; Kubota and Ishizaki, 1991]. Peak plasma concentrations of benzoic acid increased with increasing dose, while peak

hippuric acid concentrations did not change. The data suggest that the conjugation with glycine to form hippuric acid is a saturable process in humans.

Doses of 2,000-5,000 mg sodium benzoate were orally administered to male volunteers [Amsel and Levy, 1969]. At 5,000 mg, a 5,000 mg glycine supplement was administered one hour later and 2,000 mg supplements were given every 2 hours thereafter. Benzoate was excreted mainly as hippuric acid. No free benzoic acid was detected. Minor amounts of benzoyl glucuronide were detected, with more formed at the highest dose. Glycine supplementation increased the rate of hippuric acid excretion, indicating that at high dose levels, glycine is rate limiting for formation of hippuric acid.

Administration of daily oral doses of 5,330-6,000 mg 2,4-dihydroxybenzoic acid in 1,000 mg doses every 3 hours for 2 to 16 days to patients for the treatment of rheumatic fever resulted in average daily urinary excretion rates of 42.7-75.8 % [Clarke *et al*., 1958]. Average daily excretion of sulfate conjugate was relatively constant during the study, but average daily excretion of glucuronic acid conjugate increased 4- to 6-fold over the 16-day period.

In humans, an oral dose of 100 mg 4-hydroxy-3-methoxybenzaldehyde dissolved in water revealed an increase in the 4-hydroxy-3-methoxybenzoic acid output in the urine from a background level of 0.3 mg/24 hours to 96 mg/24 hours [Dirscherl and Wirtzfeld, 1964]. The observed increase was approximately 94% of the parent aldehyde dose.

2.4.3.5 Fish

Pharmacokinetic and metabolic studies have been performed on two fish species. In channel catfish, intravascular (iv) or peroral administration of a 10 mg/kg dose of [^{14}C]-benzoic acid was rapidly absorbed and eliminated. After iv dosing, elimination half-life was 5.9 hours, total body clearance was 61 ml/min., and volume of distribution was 369 ml/hr/kg. After oral administration, absorption half-life was only 0.8 hours and bioavailability was greater than 95%. Greater than 80% of the iv dose was excreted *via* the renal pathway within 24 hours. The major excreted metabolite was the taurine conjugate of benzoic acid [Plakis and James, 1990]. Being a more polar acid, terephthalic

acid, the *in vivo* metabolite of methyl 4-formylbenzoate is anticipated to undergo even more rapid excretion.

In the southern flounder, greater than 95% of a 15 mg dose of [^{14}C]-benzoic acid given by intramuscular injection was excreted as the taurine conjugate of benzoic acid in the urine. [James and Pritchard, 1987]. The rate of excretion was slow, approximately 10% per day. A subsequent investigation of the transport of benzoic acid, benzoyltaurine, and hippuric acid revealed that, at 100 uM, conjugation of benzoic acid with taurine was slow and there was also saturation of the transport of benzoyltaurine by isolated renal tubules. The amino acid conjugation (e.g., taurine) of benzoic acid has also been studied in rainbow trout (*Salmo gairdneri*) [Burke *et al*., 1987]. Greater than 99% of the radioactivity derived from a 10 mg/kg dose of [^{14}C]-benzoic acid was given by gelatin capsule was excreted in the urine within 48 hours. Greater than 98% of the excreted radioactivity was accounted for by a single metabolite, benzoyltaurine. Based on these studies, it is concluded that once benzoic acid has been absorbed by fish, is rapidly excreted as the taurine conjugate.

2.4.3.6 Multiple Species

Hippuric acid was the primary urinary metabolite following oral administration of 1-400 mg/kg bw of [^{14}C]-benzoic acid to various species including primates, pigs, rabbits, rodents, cats, dogs, hedgehogs, bats, birds, and reptiles [Bridges *et al*., 1970]. The ornithine conjugate of benzoic acid, ornithic acid, was the major urinary metabolite excreted within 24 hours in chickens and reptiles. Benzoyl glucuronide was predominant in the fruit bat. In humans, greater than 99% of ^{14}C was excreted as hippuric acid within 24 hours.

Based on extensive data for terephthalic acid and its precursor, various benzoate and benzaldehyde derivatives, it is concluded that methyl 4-formylbenzoate is hydrolyzed to 4-formylbenzoic acid that is then oxidized rapidly *in vivo* to yield terephthalic acid. This acid is the predominant plasma metabolite, which is rapidly excreted either free or conjugated in the urine. Therefore, data on the principal metabolite (terephthalic acid) and a precursor (dimethyl terephthalate) of this metabolite is directly related to the hazard

assessment of methyl 4-formylbenzoate. Also, toxicologic data on the mono-functional analogs (methyl benzoate and benzaldehyde) that participate in the same metabolic pathways of detoxication present a conservative estimate of toxic potential for methyl 4-formybenzoate. These data have also been included in the test plan and robust summaries.

3 TEST PLAN

3.1 PHYSICAL AND CHEMICAL PROPERTIES

3.1.1 Melting Point

Literature values from reliable sources are available for methyl 4-formylbenzoate and its related substances. For methyl 4-formylbenzoate, the reported value of 60-62 ^{o}C [Aldrich Chemical Co., 1986] and the calculated value of 40.11 ^{o}C [MPBPWIN EPI Suite, 2000] are in reasonable agreement. Measured melting points for the principal *in vivo* metabolite terephthalic acid is greater than 300 to 425 ^{o}C [Bemis *et al*., 1982; Anon, 1988; ICI Chemicals & Polymers, Ltd., 1991; CRC Handbook, 2000].

3.1.2 Boiling Point

For methyl 4-formylbenzoate, the reported value of 265 ^{o}C [Aldrich Chemical Co., 1986] and the calculated value of 261.31 ^{o}C [MPBPWIN EPI Suite, 2000] confirm consistency.

3.1.3 Vapor Pressure

Based on the input parameters of reported boiling point (265 ^{o}C) and melting point (61 ^{o}C), the calculated vapor pressure for methyl 4-formylbenzoate is 0.00662 mm Hg (0.00088 kPa) at 25 ^{o}C [MPBPVPWIN EPI Suite, 2000]. The measured value for a structurally related substance dimethyl terephthalate, in which the aldehyde group of methyl 4-formylbenoate is replaced by a carbomethoxy group, is reported to be in a similar range (0.01 mm Hg at 25 ^{o}C or 0.00133 kPa) [Eastman Chemical Co., MSDS]. The vapor pressure of methyl 4-formylbenzoate is expected to be significantly lower than the reported vapor pressure for the mono-functional aldehyde benzaldehyde (1.27 mm Hg or 0.169 kPa) [Ambrose *et al*., 1975] and the monofunctional ester methyl benzoate (0.38 mm Hg or 0.0507 kPa) [Daubert and Danner, 1986]. Therefore, the measured vapor pressure of methyl 4-formylbenzoate is expected to be in the range of 0.001 and 0.01 mm Hg.

3.1.4 Octanol/Water Partition Coefficients

The calculated log Kow value for methyl 4-formylbenzoate is 1.55 [KOWWIN EPI Suite, 2000]. A measured Kow for the less polar structurally related substance dimethyl terephthalate is reported to be of 2.25 [Hansch *et al*., 1995] while the measured Kow values for the more polar substance terephthalic acid is in the range between 1.16 and 2.0 [Church, undated; Leo, 1978; Tomida *et al*., 1978; Dunn and Johnson, 1983; Chan and Hansch, 1985]. Given these data the anticipated log Kow value for methyl 4-formylbenoate is in the range from 1.16 to 1.55.

3.1.5 Water Solubility

The calculated water solubility value for methyl 4-formylbenzoate is 3,136 mg/L [WSKOWWIN EPI Suite, 2000]. Whereas, the measured values for terephthalic acid are in the range from 15 to 19 mg/L at 10-25 ^{o} C [ICI Chemicals & Polymers, Ltd., 1991; Bemis *et al.*, 1982]. A higher but somewhat wider range of water solubility is reported for dimethyl terephthalate. Reported water solubilities exhibit a range of values from 19 to 37.2 mg/L [Montefibre Spa, undated; Kuhne, R. *et al.*, 1995; Eastman Kodak Co. Environmental Safety Data Sheet; undated].

3.1.6 New Testing Required

No additional testing recommended

3.2 ENVIRONMENTAL FATE AND PATHWAYS

3.2.1 Photodegradation

The calculated half-life for reaction of methyl 4-formylbenzoate with hydroxyl radicals is 7.371 hours [AOPWIN EPI Suite, 2000]. Given that the aldehyde function is more photochemically reactive than a methyl ester function, the half-life of methyl 4-formylbenzoate is anticipated to be less than that of dimethyl terephthalate. This is the case. The measured half-life of dimethyl terephthalate is approximately 3 days [Brown *et al*., 1975]. In addition, the photo-oxidation half-life of dimethyl terephthalate was reported to be 4.7 to 46.6 days [Howard *et al*., undated]. It is concluded that the half-life of methyl 4-formylbenzoate is less than 1 day.

3.2.2 Stability in Water

The hydrolysis of methyl 4-formylbenzoate has been measured over the pH range of 4 to 9. Greater than 50% hydrolysis to yield 4-formylbenzoic acid was observed after 2.4 hours at pH=9, indicating the half-life of the ester is less than 1 day at slightly basic pH. The estimated half-life at pH=7 is estimated to be approximately 200 days [Hoffman, 2003]. These experimental data are in good agreement with calculated hydrolysis data. Hydrolysis of methyl 4-formylbenzoate to yield 4-formylbenzoic acid has a half-life of 23.9 days at pH=8 and 239 days at pH=7 [HYDROWIN EPI Suite, 2000]. The measured half-life of dimethyl terephthalate in water has been reported as 1 to 4 weeks in surface water, 2 to 8 weeks in ground water and 321 days in neutral water [Howard *et al*., undated; Mabey and Mill, 1978].

3.2.3 Biodegradation

Methyl 4-formylbenzoate was predicted to be readily degradable by model calculations [BIOWIN EPI Suite, 2000]. Measured values of biodegradability data for terephthalic acid, benzaldehyde, and methyl benzoate indicate all substances are readily and ultimately biodegradable using a standard OECD 301B test or 301F protocol [Gerike and Fischer, 1979; Quest International Ltd., 1995; Corby, 1995; Amoco Chemicals Co., 1992;

Amoco Corporation, 1991]. The parent acid benzoic acid and its sodium salt were readily biodegradable in a COD (chemical oxygen demand) test [Birch and Fletcher, 1991; Pitter, 1976]. Since hydrolysis of the esters and ready oxidation of the aldehydes yields corresponding acid derivatives, the data on benzoic acid and its sodium salt validate the observations that terephthalic acid (the product of aldehyde oxidation and ester hydrolysis) is also readily biodegradable.

3.2.4 Fugacity

Transport and distribution in the environment were modeled using a combination of ECOSAR Level III EPI Suite [ECOSAR EPI Suite, 2000] and Level 1 Fugacity-based Environmental Equilibrium Partitioning Model Version 2.11 [Trent University, 1999]. The principal measured input parameters into the Trent University model are molecular weight and melting point. When measured values were unavailable, calculated data were used [ECOSAR EPI Suite, 2000]. Calculated input parameters included vapor pressure [MPBPVPWIN EPI Suite, 2000] and water solubility [WSKOWWIN EPI Suite, 2000].

The model predicts that methyl 4-formylbenzoate (1000 kg, assumed daily emission rate) is distributed mainly to the water (greater than 95%). Consistent with the high water solubility and log Kow data the distribution to the soil was only 3%. Less than 1% was distributed to air and sediment. Based on this physiochemical model, the ratio for distribution of the methyl 4-formylbenzoate between water (greater than 95%) and fish (0.00017 %) is greater than four orders of magnitude suggesting low bioaccumulation in fish.

The significance of these calculations must be evaluated in the context that methyl 4-formylbenzoate is readily hydrolyzed and oxidized to yield terephthalic acid. The model does not account for the influence of this chemical reactivity on partitioning in the environment. Therefore, the relevance of fugacity calculations for methyl 4-formylbenzoate must be evaluated in the context of these factors.

3.2.5 New Testing Required

None required.

3.3 ECOTOXICITY

3.3.1 Acute Toxicity to Fish

Based on aldehyde ECOSAR Class, 96-hour LC50 for methyl 4-formylbenzoate was calculated to be 19 mg/L. Based on ester ECOSAR Class, 96 hour LC50 was calculated to be 43 mg/L. Experimental LC50 data available on the structural relatives are in the same range as the calculated LC50 for methyl 4-formylbenzoate.

Dimethyl terephthalate exhibited 96-hour LC50 values in the same range as the values calculated for methyl 4-formylbenzoate. In static tests with fathead minnows, the 96-hour LC50 for dimethyl terephthalate was reported to be in the range from 9.6 to 45 mg/L [Eastman Kodak Co., 1977; 1984].

Data on the mono-functional analogs, methyl benzoate and benzaldehyde provide a basis for evaluating the toxicity of each functional group. Methyl benzoate also exhibits similar aquatic toxicity to fish. The 96-hour LC50 in Bluegill sunfish was 28.3 mg/L with a no observable effect concentration (NOEC) or 10 mg/L based on mortality and loss of equilibrium [Cunningham, 1997a]. Also, the 96-hour LC50 value for methyl benzoate is approximately 18 mg/L [ECOSAR EPI Suite, 2000]. For benzaldehyde, the calculated 96-hour LC50 model value was 13 mg/L [ECOSAR EPI Suite, 2000]. The NOEC for benzaldehyde of 1-day and 4-day larvae was reported to be less than 0.9 mg/L and the NOEC for survival of 1-day and 4-day larvae was 3.6 mg/L (first test) while the NOEC for survival in second test was 0.22 mg/L for 1-day larvae and 1.8 mg/L for 4-day and 7-day larvae [Pickering *et al*., 1996]. In a poorly documented study, a 14-day LC50 for benzaldehyde in guppies has been reported to be 1.57 micromoles/L (0.17 mg/L) [Deneer *et al*., 1988].

Since the experimental data on structural relatives and the calculated values of methyl 4-formylbenzoate are in good agreement, it is anticipated that the model 96-hour LC50

value of approximately 19 mg/L calculated for methyl 4-formylbenzoate is reliable [ECOSAR EPI Suite, 2000]. It is anticipated that the toxicity of methyl 4-formylbenzoate is less than or similar to that of the mono-functional analogs, methyl benzoate and benzaldehyde.

3.3.2 Acute Toxicity to Aquatic Invertebrates

Acute toxicity for aquatic invertebrates parallels that for fish exhibiting low experimental for toxicity. The calculated 48-hour LC50 or methyl 4-formylbenzoate in *Daphnia magna* is 16.4 mg/L [ECOSAR EPI Suite, 2000]. Experimental data for dimethyl terephthalate (methyl 1,4-dibenzoate) exhibits a similar order of toxicity. In *Daphnia magna*, the 48-hour static EC50 and LC50 were reported to be greater than 30 and 30.4 mg/L, respectively [Eastman Kodak Co., 1984; DuPont Chemicals, MSDS undated]. In *Daphnia magna*, the 96-hour static LC50 values were reported to be up to greater than 100 mg/L [Eastman Kodak Co., 1977]

Data for mono-functional analogs support a low order of toxicity for methyl 4-formylbenzoate. The 48-hour EC50 for methyl benzoate has been reported to be 32.1 mg/L in *Daphnia magna* [Cunningham, 1997b]. The 48-hour LC50 model value for methyl benzoate was calculated to be 84 mg/L [ECOSAR EPI Suite, 2000]. The 24-hour LC50 for benzaldehyde to *Daphnia magna* has been reported as 50 mg/L [Bringmann and Kuehn, 1977]. The calculated 48-hour LC50 model value for benzaldehyde was 12 mg/L [ECOSAR EPI Suite, 2000].

Experimental data adhering to OECD Guideline 202 are available for terephthalic acid a reaction product of methyl 4-formylbenzaldehyde. In a static test with *Daphnia magna*, the 48-hour EC50 and the NOEC for terephthalic acid were reported to be greater than 1,000 (nominal) mg/L and 600 (nominal) mg/L, respectively [Amoco Corporation, 1993b].

Based on the calculated EC50 value for methyl 4-formylbenzoate and the experimental EC50 and LC50 for methyl benzoate, benzaldehyde, and dimethyl terephthalate, it is concluded that methyl 4-formylbenzoate exhibits an EC50 in the range of 10-50 mg/L.

As for fish toxicity, it is also anticipated that the toxicity of methyl 4-formylbenzoate is less than or similar to that of the mono-functional analogs, methyl benzoate and benzaldehyde.

3.3.3 Acute Toxicity to Aquatic Plants

The model 96-hour EC50 for methyl 4-formylbenzoate was calculated to be 204 mg/L [ECOSAR EPI Suite, 2000]. In GLP-quality studies, terephthalic acid and dimethyl terephthalate exhibit very low and moderate toxicity, respectively, in aquatic plants. In a static growth inhibition study with algae conducted under OECD Guideline 201, the 96-hour EC50 and NOEC for terephthalic acid were both greater than 1000 (nominal) mg/L [Amoco Corporation, 1993c]. For dimethyl terephthalate, the 72-hour EC50 for algae growth in an EEC Directive 88/302 study was reported to be greater than the highest concentration tested (32.3 mg/L) and the NOEC was 10.8 mg/L [Huls AG, 1993].

Benzaldehyde stimulated the respiration of cells from *Chlorella vulgaris* in a dose dependent manner, but inhibited growth 30% after 80 hours and 10% after 160 hours at a concentration of 17 mg/L [Dedonder and Van Sumere, 1971]. Oxygen uptake was maximal at lower pH (pH 5.6 versus 7.2) and higher concentrations (0.001 M or 170 mg/L). The 96-hour EC50 model values for benzaldehyde and methyl benzoate were 152 and 1.4 mg/L, respectively [ECOSAR EPI Suite, 2000].

Based on the low orders of toxicity for terephthalic acid, dimethyl terephthalate and the mono-functional analog benzaldehyde, it is concluded that EC50 of methyl 4-formylbenzoate in algae is in the range of 20 to 200 mg/L.

3.3.4 New Testing Required

There are sufficient fish and invertebrate acute toxicity data for the structurally related substances and mono-functional analogs that are consistent with model values. No additional studies are recommended.

Acute plant toxicity studies for terephthalic acid, dimethyl terephthalate, and benzaldehyde indicate EC50 values greater than 20 mg/L. The calculated value of 204

mg/L supports a low order of toxicity to aquatic plants. No additional studies are required for methyl 4-formylbenzoate.

3.4 HUMAN HEALTH DATA

Hazard assessment data is presented on methyl 4-formylbenzoate, its principal *in vivo* metabolite (1,4-benzenedicarboxylic acid or terephthalic acid), a structurally related substance (dimethyl terephthalate) that also forms 1,4-benzenedicarboxylic acid *in vivo*, and two substances that are mono-functional analogs of methyl 4-formylbenzoate, benzaldehyde and methyl benzoate. Based on extensive database of information (WHO Technical Information Series, 2001) it is anticipated that the toxicity of methyl 4-formylbenzoate is less than or similar to that of the mono-functional analogs.

3.4.1 Acute Toxicity

Oral and intraperitoneal LD50 values are available for methyl 4-formylbenzoate. In rats and mice, the oral LD50 values ranged from 1600 to 3200 mg/kg bw demonstrating the low toxicity of this substances. Similar oral LD50 values have also been reported in rats and guinea pigs for benzaldehyde and methyl benzoate and in mice and rabbits for methyl benzoate [Graham and Kuizenga, 1945; Smyth *et al*., 1954; Sporn *et al*., 1967; Jenner *et al*., 1964; Kravets-Bekker and Ivanova, 1970]. High oral LD50 values (greater than 5000 mg/kg bw) have been reported in rats orally exposed to terephthalic acid and dimethyl terephthalate [Krasavage *et al*., 1973; Amoco Corporation, 1990].

Oral LD50 studies are available for methyl 4-formylbenzoate and its structural relatives. Most of the data were obtained prior to GLP and OECD Guidelines. However, the data mutually confirm that methyl 4-formylbenzoate exhibits a low order of acute toxicity. No further studies of acute toxicity are recommended.

3.4.2 Genetic Toxicity

Overall, *in vitro* and *in vivo* genotoxicity studies have been conducted with a variety of aromatic substances substituted with methyl ester and aldehyde functional groups. Data exist for the mono-functional analogs, benzaldehyde and methyl benzoate as well as for the difunctional analogs, terephthalic acid and methyl terephthalate. The results of these studies were predominantly negative, as described below. Most importantly, *in vivo*

studies have all yielded negative results. These negative *in vivo* genotoxicity assays are supported by the lack of tumorigenicity in chronic animal studies with members of this group. Therefore, the database on genetic toxicity of the structurally related benzyl derivatives is adequate to support the low genotoxic potential of methyl 4-formylbenzoate.

3.4.2.1 In Vitro

In vitro genetic toxicity data are available on structurally related substances, benzaldehyde, methyl benzoate, terephthalic acid, and dimethyl terephthalate. The vast majority of standardized *in vitro* genotoxicity assays (Ames (AMS), mouse lymphoma (MLA), sister chromatid exchange (SCE), chromosomal aberration (ABS), and unscheduled DNA synthesis (UDS)) show no evidence of genotoxicity.

The above substances were non-mutagenic in all standard plate incorporation and/or pre-incubation Ames assays using *Salmonella typhimurium* strains TA92, TA94, TA97, TA98, TA100, TA102, TA104, TA1535, TA1537, and TA1538, when tested at concentrations ranging up to the level of cytotoxicity or at ICH/OECD-recommended maximum test concentrations, both in the absence and presence of metabolic activation (S9 fraction) [Sasaki and Endo, 1978; Florin *et al*., 1980; Rapson *et al*., 1980; Kasamaki *et al*., 1982; Zeiger *et al*., 1982, 1992; Wiessler *et al.*, 1983; Heck *et al*., 1989; NTP, 1990; Monarca *et al.*, 1989; 1991; Dillon *et al*., 1992, 1998]. Additional Ames tests on metabolites isolated from the urine of rats administered benzaldehyde by oral gavage also were negative in *Salmonella typhimurium* strains TA98 and TA100, both with and without metabolic activation [Rockwell and Raw, 1979]. Mutation or DNA repair assays using *Escherichia coli* strains WP2 uvrA or Sd-4-73 with methyl benzoate [Szybalski, 1958] also showed no evidence of genotoxicity.

Negative results were obtained with benzaldehyde in the Rec DNA repair assay using *Bacillus subtilis* strains H17 and M45, whereas weakly positive results were obtained with metabolically activated benzaldehyde [Oda *et al*., 1978; Matsui *et al.*, 1989].

In vitro assays in isolated mammalian cells produced both negative and positive results. Benzaldehyde exhibited evidence of mutagenicity in the forward mutation assay with L5178Y mouse lymphoma cells (MLA), both with and without metabolic activation [McGregor *et al*., 1991; Heck *et al*., 1989]. Dimethyl terephthalate did not alter mutation frequency with or without metabolic activation [Myhr and Caspary, 1991].

In cytogenetic tests performed in Chinese hamster ovary and fibroblast cell lines, both positive and negative results were reported with benzaldehyde, with the positive result usually occurring at the higher culture concentrations in the ABS assay [Kasamaki *et al.*, 1982; Sofuni *et al*., 1985; Galloway *et al*., 1987]. Both dimethyl terephthalate and terephthalic acid produced negative results when tested in the ABS assay using human peripheral blood lymphocytes [Monarca *et al.*, 1989; 1991]. Dimethyl terephthalate was also negative in CHO cells in the presence or absence of metabolic activation [Loveday *et al*., 1990].

The authors of the MLA and ABS assays [Heck *et al*., 1989] have emphasized that the positive results in the MLA and ABS assays may be artifacts resulting from changes in culture pH and osmolality. Treatment with high dose levels of substances (e.g., reactive aldehydes and carboxylic acids) with the potential to alter acidity or osmolality may induce a significant increase in mutant frequencies or aberrations in these assays. Often the results are inconsistent with the results of other genotoxicity assays (i.e., AMS and UDS) [Heck *et al.,* 1989].

In the SCE assay, equivocal results were reported for benzaldehyde in CHO cell lines and in human lymphocytes [Galloway *et al*., 1987; Sasaki *et al*., 1989; Jansson *et al.,* 1988]. Negative results were obtained in this assay for dimethyl terephthalate (CHO cells) [Jansson *et al*., 1988; Loveday *et al*., 1990].

No UDS was observed in rat hepatocytes exposed to benzaldehyde [Heck *et al*., 1989] nor in human HELA or hamster embryo cells exposed to dimethyl terephthalate [Monarca *et al.*, 1989; 1991].

In summary, data available for approximately 30 *in vitro* genotoxicity assays for structural relatives or metabolites of methyl 4-formylbenzoate indicate a low genotoxic potential for this chemical.

3.4.2.2 In Vivo

In vivo mutagenicity and genotoxicity data exist for the structurally related substances (terephthalic acid, dimethyl terephthalate, and benzaldehyde).

None of these substances showed any evidence of genotoxicity in well-recognized *in vivo* assays (mouse micronucleus and sex-linked recessive lethal). In mammals, substances were administered by intraperitoneal injection at doses that were significant fractions of the reported lethal dose levels.

Mouse micronucleus tests were consistently negative with dimethyl terephthalate and terephthalic acid [Shelby *et al*., 1993; Bioreliance, 2001] with the exception of one study testing dimethyl terephthalate administered in DMSO at high dose levels [Goncharova *et al*., 1988]. The positive finding in the Goncharova *et al*. (1988) study was considered by the authors to be unusual and perhaps related to a reaction between the solvent vehicle (DMSO) and the test material (dimethyl terephthalate).

In the (sub-mammalian) sex-linked recessive lethal mutation assay in fruit flies (*Drosophila melanogaster*), negative results were obtained with dimethyl terephthalate and benzaldehyde either after feeding or administration by intraperitoneal injection [Woodruff *et al*., 1985].

Given that the *in vitro* and *in vivo* results both consistently demonstrate that the substances related to methyl 4-formylbenzoate exhibit a low order of genotoxic potential, no additional studies are required for this chemical.

3.4.3 Repeated Dose Toxicity

Studies examining possible subacute and subchronic toxic effects are available on the principal metabolite (terephthalic acid), dimethyl terephthalate, benzaldehyde, and methyl benzoate. Taken together, these data indicate a low order of subchronic toxicity for methyl 4-formylbenzoate. Long term studies on dimethyl terephthalate, benzaldehyde, benzoic acid and its sodium salt provide adequate evidence that methyl 4-formylbenzoate, its principal metabolite, related substances (dimethyl terephthalate), and mono-functional analogs all exhibit no significant carcinogenic potential in animals.

3.4.3.1 Subacute Studies

3.4.3.1.1 Rats

In preliminary dose range-finding studies [NTP, 1990], benzaldehyde was administered to rats by corn oil gavage for 14-16 days at doses up to 2,000 mg/kg bw/day. The no-observed-adverse-effect level (NOAEL), determined from this study based on increased mortality, was 400 mg/kg bw/day for benzaldehyde.

In addition to oral exposure, benzaldehyde has been tested in rats through inhalation. The 14-day inhalation study [Laham *et al*., 1991] with benzaldehyde showed overall, mild irritation of the nasal mucosa, effects of the central nervous system, and some hematological and biochemical effects at exposures between 500 and 1,000 ppm was reported. Exposed male rats, but not female rats, showed goblet cell metaplasia thought to be related to adaptation following exposure to benzaldehyde.

Dimethyl terephthalate was fed to rats for 14 days at dietary concentrations of up to 3% resulting in an increase in the incidence of bladder calculi at the higher doses [Chin *et al*., 1981]. Rats with calculi had grossly observable irregular thickening of the bladder wall. Bladder calculi were composed of calcium and terephthalic acid with 5-7% protein. Similar effects were reported in F344 rats maintained on a diet of terephthalic acid [Chin *et al*., 1981].

In a 28-day inhalation study, rats exposed to 21.5 mg terephthalic acid/m^3 for 6 hours/day, 5 days/week showed no adverse effects [Amoco Corporation, 1973].

3.4.3.1.2 Mice

The preliminary testing conducted by the National Toxicology Program (NTP) also included a gavage mouse study with benzaldehyde [NTP, 1990]. Mice were administered benzaldehyde for 14-16 days at doses of up to 3,200 mg/kg bw/day. Based on increased mortality, the NOAEL was determined to be 400 mg/kg bw/day for benzaldehyde.

3.4.3.2 Subchronic Studies

3.4.3.2.1 Rats

When benzaldehyde was administered by gavage to rats for 13 weeks [NTP, 1990], survival and body weights were reduced at the highest dose tested (800 mg/kg bw/day). Also at the high dose, multiple histopathological effects were reported in the brain, forestomach, liver, and kidney. Based on the various lesions reported at the high dose, the NOAEL was determined to be 400 mg/kg bw/day and doses selected for a 2-year study were 200 and 400 mg/kg bw/day.

In addition to the NTP study, benzaldehyde has been tested in 2 other studies [Sporn *et al*., 1967; Hagan *et al*., 1967] reported with limited experimental detail and prior to the establishment of GLP guidelines. In a study [Sporn *et al*., 1967], adult white rats were orally administered doses of 10 mg benzaldehyde diluted in 0.1 ml of oil on alternate days for a period of 8 weeks. No hepatic enzyme activity was reported. The authors conducted a second investigation lasting 12 weeks in which no effects on growth, liver or adrenal gland weight were reported. In a study conducted by the FDA, benzaldehyde was fed to groups of Osborne-Mendel rats at concentrations of 0 or 10,000 ppm (approximately 500 mg/kg bw/day) for 16 weeks or 0 or 1,000 ppm (approximately 50 mg/kg bw/day) for 27-28 weeks [Hagan *et al*., 1967]. No clinical, hematological or histopathological effects were reported.

Methyl benzoate administered to rats (route not specified) for 45 days at doses of 111 or 500 mg/kg bw/day, did not produce any histological findings, but was reported to produce some effects on blood parameters [Kravets-Bekker and Ivanova, 1970].

Rats were fed 0, 05, 0.16, 0.50, 1.6, or 5.0% terephthalic acid in the diet for 15 weeks [Amoco Corporation, 1970]. There were no effects on feed intake, hematology, clinical chemistry, or organ weights. At the highest dose, 3 females died (cause unknown), body weights were mildly depressed, hematuria was noted on a sporadic basis in males, "small" occult blood was reported during urinalysis in both sexes, increased incidence of bladder calculi in males was noted, and significantly increased incidence and severity of proliferative changes (hyperplasia) in the urinary bladder and occasionally kidney pelvis epithelium of males was reported. One male rat at the mid-dose also died (cause unknown). The microscopic pathology, although noted in all groups (including controls), was only statistically significant in high-dose males. A NOAEL of 1.6% (approximately 1220 and 1456 mg/kg bw for males and females, respectively) reported by the authors was based on bladder calculi and subsequent hyperplasia.

In a 90-day dietary study, rats were initially fed 5% terephthalic acid for the first week of the study, but it was reduced to 3% for the remainder of the study [Amoco Corporation, 1972]. Bladder stones were reported in 11/18 males and 3/19 females. In addition, 13/18 males and 3/19 females were reported to have mild to moderate hyperplasia of the bladder urothelium. Eight out of 13 males (62%) and 3/3 (100%) females with transitional cell hyperplasia also had bladder stones consisting of calcium terephthalate and protein.

3.4.3.2.2 Mice

Mortality was also increased (9/10 males and 1/10 females died) when benzaldehyde was administered by corn oil gavage to B5C3F1 mice at the highest dose tested (1,200 mg/kg bw/day) [NTP, 1990]. At 600 mg/kg bw/day, the final mean body weight of males was 9% lower than controls. Mild to moderate renal tubule degeneration occurred in all males in the high-dose group and in 1/10 males in the 600 mg/kg bw/day group. No other

compound-related effects were reported. Based on the mild renal lesions and depressed body weight gain, the doses selected for a 2-year study were 300 and 600 mg/kg bw/day.

3.4.3.3 Chronic Studies

3.4.3.3.1 Rats

Benzaldehyde was administered at dose levels of 300 or 600 mg/kg bw in corn oil by gavage five days per week to groups of 50 F344/N rats or B6C3F1 mice for a period of 2 years [NTP, 1990]. Animals were observed once weekly for 12-13 weeks and at least monthly thereafter. All animals were subject to necropsy after death, or at the end of the study. Throughout these studies, mean body weights were comparable among all groups. Increased mortality seen in some of the groups was attributable to the gavage procedure, reflux and aspiration of the gavage material into the lungs, or administration errors resulting in direct disposition of material into the lungs. Summaries of the rat studies and results are described below and the results of the mouse studies are discussed in the section on mice.

Groups of 50 male and 50 female F344/N rats were administered 0, 200, or 400 mg/kg bw/day, 5 days/week, of benzaldehyde in corn oil by gavage for 2 years. Survival was significantly decreased in the high-dose male group after Day 373; however, there were no other compound-related effects in any of the rats. The NTP concluded that there was “no evidence of carcinogenic activity” in rats given benzaldehyde under these study conditions [NTP, 1990].

White and gray rats were administered 0.005 or 0.05 mg/kg bw/day of methyl benzoate for 6 months [Kravets-Bekker and Ivanova, 1970]. The general condition of the animals in both dose groups did not differ from controls. At the high dose, there was decrease in the number of reticulocytes (p less than 0.01) but there was no difference from controls in prothrombin time or phagocytic activity at either dose. In behavioral tests, at the high dose, the latent period for response to "bell" or "light" stimulus was increased. Also, there was an increase in the number of sulfhydryl groups in cerebral tissue of high-dose rats. At

necropsy, congestion and swelling of the hepatic central veins and capillaries was reported in high-dose rats. There were no histological findings in the low-dose animals.

In a standard cancer bioassay Fischer 344 rats were fed up to 5000 ppm dimethyl terephthalate in the diet for 2 years with no adverse effects (Federal Register Notice, 1981 – no robust summary included).

Rats fed up to 1000 mg/kg bw/day of terephthalic acid in the diet for 2 years showed no adverse effects with the exception of bladder stones in 13/126 high-dose females [Chemical Industry Institute of Technology (CIIT), 1983]. Through scheduled sacrifices at 6, 12, and 18 months, the progression to the development of the calculi was observed. No evidence of bladder stones were observed at 6 and 12 months; however, sand-like particle or bladder calculi were reported in 2 of the high-dose females at 18 months.

Similar results were reported in another 2-year rat study in which rats were fed up to 5% terephthalic acid [Gross, 1974]. In this study, the highest dose (approximately 2500 mg/kg bw/day) was reported to produce reduced body weight gain in both sexes, increased kidney weight in males, increased adrenal weight in both sexes, increased incidence of bladder stones (42/47 males; 39/42 females), and increased incidence of bladder and ureter tumors (21/37 males; 21/34 females). At the 2% concentration (approximately 1000 mg/kg bw/day), there was reduced body weight gain in males, and reduced liver, kidney, and heart weight in females. The incidence of bladder stones in females fed 1% was 1/48. Bladder and ureter tumors were reported as 1/48 at 2% in males, 2/48 at 2% in females and 1/43 at 1% in males.

3.4.3.3.2 Mice

Groups of 50 male B6C3F1 mice were administered 0, 200, or 400 mg/kg bw/day, 5 days/week of benzaldehyde in corn oil by gavage for 2 years. Groups of 50 female mice were administered 0, 300, or 600 mg/kg bw/day of benzaldehyde. There were no compound-related clinical signs or effects on body weight, and survival was not affected by treatment. A non-statistically significant increase in the incidence of forestomach focal hyperplasia was reported in both sexes. An increase in the incidence of squamous cell

papillomas of the forestomach was reported in both sexes at all doses tested and reached statistical significance in the female mice. There was no increase in the incidence of squamous cell carcinomas of the forestomach in either sex. The NTP considered the increase in forestomach papillomas to be attributable to a concurrent increase in hyperplasia as a result of benzaldehyde treatment and, therefore, concluded that there was "some evidence of carcinogenic activity" in mice under these study conditions [NTP, 1990].

The occurrence of squamous cell papillomas and forestomach hyperplasia in rodents is common in NTP bioassay gavage studies in which a high concentration of an irritating material in corn oil is delivered daily by needle into the forestomach for two years. High concentrations of aldehydes such as malonaldehyde, furfural, and benzaldehyde (NTP 1988, 1990, 1993 - no robust summaries prepared) and other irritating substances including dihydrocoumarin and courmarin (NTP 1990, 1992 - no robust summaries prepared) delivered in corn oil by gavage are consistently associated with these phenomena in the forestomach of rodents. Squamous cell papillomas are benign lesion of surfaces covered with squamous epithelium. A majority of papillomas arise as a result of chronic irritation, or from infection from some strains of viruses (Smith and Ford, 1993 - no robust summary prepared). Additionally, forestomach hyperplasia and papillary proliferation in these studies did not progress to squamous cell carcinomas.

Apparently, the combination of daily introduction of a dosing needle into the forestomach and delivery of a high concentrations of an irritating test material in corn oil, which itself is a mild irritant and mitogen, was the likely source of the papillomas in the rodent forestomach. This conclusion is supported by the observation that the occurrence of squamous cell papillomas and forestomach hyperplasia in gavage administration of a test material in corn oil for 2 years (see below; NTP, 1986 - no robust summary prepared) disappear when the same substance is administered at similar intake levels in the diet (NTP, 1993 - no robust summary prepared). Therefore, the appearance of these benign lesions in the 2-year rodent bioassay have no relevance to humans, given that human exposure occurs when low levels of benzaldehyde are consumed in the diet.

In conclusion, evidence of carcinogenicity in the gavage benzaldehyde study is associated with the repeated gavage administration of high dose levels of test substance in a corn oil vehicle or a statistical anomaly. The above observations strongly suggest that the results of the gavage NTP studies have no significance to humans.

This conclusion is further supported by the lack of tumorigenicity in a chronic studies conducted with a structural representative of this group, sodium benzoate, and the primary metabolite, benzoic acid. No effect on tumor incidence or survival was seen in male and female albino Swiss mice administered 2% sodium benzoate in drinking water (approximately 4,000 mg/kg bw/day) for their life span (up to approximately 112 weeks) [Toth, 1984]. The only reported finding in a 17-month study in which mice were orally administered 40 mg/kg bw/day of benzoic acid was increased survival as compared to controls [Shtenberg and Ignat'ev, 1970].

In a standard cancer bioassay B6C3F1 mice were fed up to 5000 ppm dimethyl terephthalate in the diet for 2 years with no adverse effects with the exception of a statistically significant increase in lung tumors in treated male mice [Federal Register, 1981 – no robust summary prepared]. The authors reported that the increased lung tumor incidence in male mice has been peer reviewed a few times and it was finally concluded that this finding was considered biologically equivocal due to the lack of similar findings in female mice and an exceptionally low incidence of lung tumors in control males.

3.4.4 Reproductive Toxicity

Studies examining possible reproductive toxicity are available on the principal metabolite (terephthalic acid), dimethyl terephthalate and benzaldehyde.

Male rats had been fed 0.25, 0.50, or 1.0% dimethyl terephthalate in the diet for 115 days were mated with females, which had been fed the same diets for 6 days [Krasavage *et al*., 1973]. Females were maintained on the treated diets throughout gestation, parturition, and lactation. No effects on fertility, reproductive capacity, libido, pregnancy, gestation, litter size, or pup viability were reported. Significantly lower average pup body weights at weaning were reported in offspring of rats fed 0.5 or 1.0% dimethyl terephthalate

compared to controls. The authors suggested that the decreased pup body weight was related to lactation exposure to dimethyl terephthalate or its metabolite terephthalic acid plus access to treated diet.

In a GLP-compliant study, 2 strains of rats (Wistar and CD) were compared in a 1-generation study testing terephthalic acid fed at dietary concentrations up to 5% (approximately 2500-3000 mg/kg bw/day) [Chemical Industry Institute of Technology (CIIT), 1982]. Parental rats were fed terephthalic acid 90 days prior to mating and throughout mating. Maternal exposure continued throughout gestation and lactation and offspring exposure continued to 30 days post-weaning. Parameters evaluated included fertility index, number of offspring born/dam, number and proportion of each sex born, number (Day 0, 1, and 21) and proportion (Day 1 and 21) of each sex alive, and average weight at Day 1 and 21 of all offspring and of each sex. At study termination, all offspring were killed, grossly examined and necropsied. Body weights were significantly decreased after 13 weeks at 2 and 5% in both sexes of CD rats, at 0.03% in CD males and at 5% in Wistar rats of both sexes. At 5%, death occurred in 3 CD female and 1 Wistar rat/sex. During the one-generation component of the study 3 CD rats (1 male at 2% and 1/sex at 5%) and 4 female Wistar rats (2 at 5% and 2 at 0.03%) died. No effect on fertility index or litter size was reported. No effects on litter size, sex ratio, or total number of offspring were reported. On Day 0, 17 Wistar offspring (1 at 0.03%, 2 at 0.125%, 1 at 0.5%, 12 at 2% [2 from 1 dam, 10 from another]) and 23 CD offspring (1 at 0.5%, 7 at 2% [3 dams] and 15 at 5% [3 dams; with 11 from 1 of them]) were found dead. No statistical differences were reported in viability of either strain on Days 0, 1, or 21. Survival on Day 21 of CD offspring of rats fed 5% was reduced. On Day 1, body weights were reduced in Wistar rats at 5%. On Day 21, body weights were reduced in both rat strains at 5%. At these levels, several pups were not allowed to nurse by dams showing signs of toxicity and several large litters were lost. During the post weaning period (Day 21-51), 18 Wistar and 16 CD rats at 5% died. A high incidence of renal and bladder calculi were reported in these animals. Renal and bladder calculi also were reported in all necropsied rats fed 5% terephthalic acid. The parental NOAEL was reported to be 0.5 and 2.0% for CD and Wistar rats, respectively. The reproductive NOAEL for both strains was greater than 5.0%. The F1 offspring NOAEL was reported to be 0.5% for both strains.

Approximately 5 mg/kg bw/day of benzaldehyde was administered by gavage to 10 breeding age rats every other day for a period of 32 weeks [Sporn *et al*., 1967]. Two pregnancies per rat were studied, one at 75 days and one at 180 days. There was no statistical significant difference between treatment and control groups. It was reported that fewer females in the treated group became pregnant; however, no data or statistical analyses were performed, and the authors concluded that treatment did not cause a significant change in any of the reproductive parameters measured.

3.4.5 Developmental Toxicity

Developmental toxicity has been tested in terephthalic acid, the *in vivo* metabolite of methyl 4-formylbenzoate. Also included are data for dimethyl terephthalate, a substance that also forms terephthalic acid *in vivo*, and benzyl alcohol, a metabolic precursor of the mono-functional analog benzaldehyde.

Overall, the substances from this group were tested for developmental toxicity with uniform results that indicate no teratogenic potential in the absence of maternal toxicity.

3.4.5.1 Rats

Pregnant Wistar rats were gavaged with 1000 mg/kg bw/day of dimethyl terephthalate throughout gestation Days 7-16 and killed on Day 21 [Hoechst, 1986]. There were no signs of maternal toxicity and no abnormal developmental effects and no pre- or post-implantation losses were reported.

In a GLP-compliant study, pregnant rats underwent whole body inhalation exposures of 1.0, 5.0, or 10.0 mg/m^3, 6 hours/day of terephthalic acid throughout gestation Days 6-15 [Amoco Corporation, 1989b]. Rats were killed on Day 21 and "standard" guideline postmortem exams were conducted on dams and fetuses. No maternal deaths were reported and there were no significant differences in clinical signs, mean body weight or weight gain, uterine weight or implant number compared to controls. No statistically significant differences from control were reported in mean litter weights, pup viability, or number of fetal malformations. There was no difference from control noted in external

soft tissue examination; however, there was a slight increase in the incidence of rib anomalies (all types added together) at 5.0 mg/m^3. The rib anomalies reported at the middle dose were not considered to be an indicator of teratogenicity since they are a common variation, were not dose-dependent, were not accompanied by other signs of embryotoxicity, and were within the range of historical controls for the laboratory.

3.4.5.2 Mice

In a teratology study, groups of pregnant CD-1 mice were administered 0 or 550 mg/kg bw/day of benzyl alcohol in corn oil by gavage during gestation Days 6-15 [York *et al.*, 1986]. Body weight, clinical observations, and mortality were recorded daily throughout treatment and up to 3 days postpartum. All parameters tested, including gestation index, average number of live pups/litter, postnatal survival, and pup body weight, were statistically similar for the treated and control animals.

Groups of CD-1 mice were gavaged with 750 mg/kg bw/day of benzyl alcohol on gestation Days 6-13 [Hardin *et al.*, 1987]. Controls received distilled water only. Clinical signs of maternal toxicity were reported and included hunched posture, tremors, inactivity, prostration, hypothermia, ataxia, dyspnea, swollen or cyanotic abdomen, and piloerection. There was no significant difference in maternal body weight measured on Days 4 and 7 of gestation between treated and control animals; however, statistically significant decreases were observed in treated females on gestation Day 18 and Day 3 postpartum. Maternal body weight gain during Days 7-18 of gestation was also significantly lower than that of controls. Significant differences were also observed in pup body weight and weight gain, including mean pup weight per litter, mean litter weight change, and mean pup weight change (between Day 1 and 3 postpartum). No differences were observed in the mating or gestation indices, the total number of resorptions, the number of live pups per litter, or in pup survival. Eighteen deaths were reported during the treatment period and they were all attributed to the treatment. One more death was reported the day after treatment was terminated. Although the authors concluded that benzyl alcohol was a potential reproductive hazard, the effects observed were in conjunction with significant maternal toxicity.

3.4.6 New Testing Required

Numerous genetic, acute, repeat-dose, developmental, and reproductive toxicity studies exist for the principal metabolite, metabolic precursors of that metabolite, and other structurally related mono-functional analogs. Toxicological data on these substances are directly related to the evaluation of methyl 4-formylbenzoate. Moreover, the dose levels tested provide adequate margins of safety to accommodate any differences in structure between methyl 4-formylbenzoate and these substances.

The only significant effect in any of these studies is the development of renal calculi and renal tumors in a chronic rat study. This phenomenon is associated with the renal processing of extremely high dose levels of organic acids (*i.e.*, terephthalic acid). Chronic exposure to such acids leads to cumulative formation of renal calculi composed principally of calcium salts of these acids. Accumulation of calculi in the kidney leads to renal hyperplasia progressing eventually to tumors. These effects would not be observed in humans under normal conditions of exposure. In other studies at lower dose levels there is no evidence of the formation of renal calculi, renal hyperplasia or tumor formation.

3.5 TEST PLAN TABLE

Chemical	Physical-Chemical Properties				
	Melting Point	Boiling Point	Vapor Pressure	Partition Coefficient	Water Solubility
CAS No. 001571-08-0 Methyl 4-formylbenzoate	A	A	Calc	Calc	Calc

Chemical	Environmental Fate and Pathways			
	Photodegradation	Stability in Water	Biodegradation	Fugacity
CAS No. 001571-08-0 Methyl 4-formylbenzoate	Calc	R, Calc	R, Calc	Calc

Chemical	Ecotoxicity		
	Acute Toxicity to Fish	Acute Toxicity to Aquatic Invertebrates	Acute Toxicity to Aquatic Plants
CAS No. 001571-08-0 Methyl 4-formylbenzoate	R, Calc	R, Calc	R, Calc

Chemical	Human Health Data					
	Acute Toxicity	Genetic Toxicity *In Vitro*	Genetic Toxicity *In Vivo*	Repeat Dose Toxicity	Reproductive Toxicity	Develop-mental Toxicity
CAS No. 001571-08-0 Methyl 4-formylbenzoate	A	R	R	R	R	R

Legend	
Symbol	**Description**
R	Endpoint requirement fulfilled using category approach, SAR
T	Endpoint requirements to be fulfilled with testing
Calc	Endpoint requirement fulfilled based on calculated data
A	Endpoint requirement fulfilled with adequate existing data
NR	Not required per the OECD SIDS guidance
NA	Not applicable due to physical/chemical properties
O	Other

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The Flavor And Fragrance High Production Volume Consortia

Eastman Chemical Company

Robust Summaries for Methyl 4-formylbenzoate

Methyl 4-formylbenzoate **CAS No. 001571-08-0**

Registration Number

Submitted to the EPA under the HPV Challenge Program by:

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The Flavor and Fragrance High Production Volume Consortia

Robust Summaries for Methyl 4-formylbenzoate

The data summarized in the test plan and data recorded in the robust summaries for structurally related substances have been previously submitted to the Office of Economic and Community Development (OECD) and the U.S. Environmental Protection Agency (EPA). Data for terephthalic acid and dimethyl terephthalate were submitted in the form of Safety Information Data Sheets (SIDS) to the OECD by the EPA. The test plans and robust summaries were accepted with no requests for additional testing. Robust summaries used in the preparation of these SIDS submissions have been included in this document.

In addition, the Flavor and Fragrance High Production Volume Consortia (FFHPVC) has submitted (12/01) a test plan and robust summaries for the chemical category named "Benzyl Derivatives" including data for ten benzyl derivatives. EPA commented (12/02) on this test plan and robust summaries. The robust summaries for methyl benzoate, benzaldehyde, benzoic acid and sodium benzoate for which no revisions or additional information were requested or ones in which requested information has been added are also included in this document.

The evaluation of the quality of the following data uses a systematic approach described by Klimisch [Klimisch *et al*., 1996]. Based on criteria relating to international testing standards for categorizing data reliability, four reliability categories have been established. The following categories are:

- Reliability code 1. Reliable without restrictions
- Reliability code 2. Reliable with restrictions
- Reliability code 3. Not reliable
- Reliability code 4. Not assignable

1 CHEMICAL AND PHYSICAL PROPERTIES

1.1 Melting Point

Substance Name	Methyl 4-formylbenzoate
CAS No.	001571-08-0
Method/guideline	Measured
Melting Point	60-62 °C
Data Qualities Reliabilities	Reliability code 1. Reliable without restriction.
Remarks for Data Reliability	Code 1. Comparable to guideline study.
References	Aldrich Chemical Co. (1986) Aldrich Catalog/Handbook of Fine Chemicals. Aldrich Chemical Co., Inc. Milwaukee, WE. P. 906#24, 474-0.

Substance Name	Methyl 4-formylbenzoate
CAS No.	001571-08-0
Method/guideline	Calculated
Melting Point	40.11 °C
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Code 4. Calculated.
References	MPBPVP EPI Suite (2000) US Environmental Protection Agency.

Substance Name	Methyl 4-formylbenzoate
CAS No.	001571-08-0
Remarks for Substance	Data are for structurally related substance terephthalic acid
Method/guideline	Measured
Melting Point	Greater than 300 °C
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Basic data given: comparable to guidelines/standards.
References	Bemis, Dindorf, Harwood, Samans. (1982) Kirk-Othmer Encyclopedia of Chemical Technology 3rd Ed. Vol 17, 734.

	Encyclopedia of Chemical Technology 3rd Ed. Vol 17, 734.

Substance Name	Methyl 4-formylbenzoate
CAS No.	001571-08-0
Method/guideline	Measured
Remarks for Substance	Data are for structurally related substance terephthalic acid
Melting Point	402 °C
Data Qualities Reliabilities	Reliability code 3. Not reliable.
Remarks for Data Reliability	Code 3. Documentation insufficient for assessment.
References	Anon (1988) Dangerous Properties of Industrial Materials Report 8, 68-71.

Substance Name	Methyl 4-formylbenzoate
CAS No.	001571-08-0
Remarks for Substance	Data are for structurally related substance terephthalic acid
Method/guideline	Measured
Melting Point	425 °C
Data Qualities Reliabilities	Reliability code 1. Reliable without restriction.
Remarks for Data Reliability	Code 1. Comparable to guideline study.
References	ICI Chemicals & Polymers Limited (1991) Product Safety Data: Pure Terephthalic Acid, Jan 1991.

Substance Name	Methyl 4-formylbenzoate
CAS No.	001571-08-0
Remarks for Substance	Data are for structurally related substance terephthalic acid
Method/guideline	Measured
Melting Point	Greater than 300 °C
Data Qualities Reliabilities	Reliability code 1. Reliable without restriction.
Remarks for Data Reliability	Code 1. Comparable to guideline study.
References	CRC Handbook of Chemistry and Physics (2000) 82nd edition, David R. Lide, editor, The Chemical Rubber Co. Press, Inc., Boca Raton, FL.

1.2 Boiling Point

Substance Name	Methyl 4-formylbenzoate
CAS No.	001571-08-0
Method/guideline	Measured
Boiling Point	265 °C
Data Qualities Reliabilities	Reliability code 1. Reliable without restriction.
Remarks for Data Reliability	Code 1. Comparable to guideline study.
References	Aldrich Chemical Co. (1986) Aldrich Catalog/Handbook of Fine Chemicals. Aldrich Chemical Co., Inc. Milwaukee, WE P. 906#24, 474-0.

Substance Name	Methyl 4-formylbenzoate
CAS No.	001571-08-0
Method/guideline	Calculated
Boiling Point	261.31 °C
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Code 4. Calculated.
References	MPBPVP EPI Suite (2000) US Environmental Protection Agency.

1.3 Vapor Pressure

Substance Name	Methyl 4-formylbenzoate
CAS No.	001571-08-0
Remarks for Substance	Data are for structurally related substance dimethyl terephthalate

	terephthalate
Method/guideline	Measured
Vapor Pressure	0.00133 kPa
Temperature	25 °C
Remarks for Results	Input parameters: BP - 179 °C. The vapor pressure of methyl 4-formylbenzoate is expected to be in the same range as that of dimethyl terephthalate.
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Basic data given: comparable to guidelines/standards.
References	Eastman Chemical Co., Material Safety Data Sheet.

Substance Name	Methyl 4-formylbenzoate
CAS No.	001571-08-0
Remarks for Substance	Data are for structurally related substance methyl benzoate
Method/guideline	Measured
Year	1986
Vapor Pressure	0.0507 kPa (0.38 mm Hg)
Temperature	25 °C
Data Qualities Reliabilities	Reliability code 1. Reliable without restriction.
Remarks for Data Reliability	Code 1. Comparable to guideline study.
References	Daubert T.E. and Danner, R.P. (1986) US EPA EPI Suite (2000) MPBPVPWIN.

Substance Name	Methyl 4-formylbenzoate
CAS No.	001571-08-0
Remarks for Substance	Data are for the structurally related substance benzaldehyde
Method/guideline	Measured
Year	1975
Vapor Pressure	0.169 kPa (1.27 mm Hg)
Temperature	25 °C
Remarks for Results	Vapor pressure for methyl 4-formylbenzoate is expected to be significantly lower than that for benzaldehyde.

Data Qualities Reliabilities	Reliability code 2. Reliable with restrictions.
Remarks for Data Reliability	Code 2. Acceptable, well-documented publication/study report, which meets basic scientific principles.
References	Ambrose D., Connett, J., Green, J., Hales, J., Head, A., and Martin, J. (1975) Thermodynamic properties of organic oxygen compounds. 42 Physical and thermodynamic properties of benzaldehyde. J. Chem. Therm., 7,1143-57.

Substance Name	Methyl 4-formylbenzoate
CAS No.	001571-08-0
Method/guideline	Calculated
Vapor Pressure	0.00088 kPa (0.00662 mm Hg)
Temperature	25 °C
Remarks for Results	Input parameters: BP - 265 °C, MP - 61 °C
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Code 4. Calculated.
References	MPBPVPWIN EPI Suite (2000) US Environmental Protection Agency.

1.4 n-Octanol/Water Partition Coefficients

Substance Name	Methyl 4-formylbenzoate
CAS No.	001571-08-0
Method/guideline	Calculated
Log Pow	1.55
Temperature	25 ° C
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Code 4. Calculated.

References	KOWWIN EPI Suite (2000) US Environmental Protection Agency.

Substance Name	Methyl 4-formylbenzoate
CAS No.	001571-08-0
Remarks for substance	Data are for structurally related substance terephthalic acid
Method/guideline	Measured
Log Pow	1.16
Data Qualities Reliabilities	Reliability code 3. Not reliable.
Remarks for Data Reliability	Code 3. Documentation insufficient for assessment.
References	Church C. Unpublished analysis Zeneca Brixham Environmental Laboratory.

Substance Name	Methyl 4-formylbenzoate
CAS No.	001571-08-0
Remarks for Substance	Data are for structurally related substance terephthalic acid
Method/guideline	Measured
Log Pow	1.19
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Acceptable, well-documented publication/study report, which meets basic scientific principles.
References	Leo A.J. (1978) Report on the calculation of octanol/water log P valves for structures in EPA files.

Substance Name	Methyl 4-formylbenzoate
CAS No.	001571-08-0
Remarks for substance	Data are for structurally related substance terephthalic acid
Method/guideline	Measured
Log Pow	1.25
Temperature	25 ° C
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Basic data given: comparable to guidelines/standards.
References	Tomida, Yotsiyanag, Ikeda. (1978) Chem Pharm Bull, 261, 2824-2831, Verschueren Handbook of Environmental Data on

	2824-2831, Verschueren Handbook of Environmental Data on Organic Chemicals, 3rd Ed.

Substance Name	Methyl 4-formylbenzoate
CAS No.	001571-08-0
Remarks for substance	Data are for structurally related substance terephthalic acid
Method/guideline	Measured
Log Pow	1.96
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Basic data given: comparable to guidelines/standards.
References	Dunn and Johnson (1983) Plank Struct Act Relat 2 156-163, Verschueren Handbook of Environmental Data on Organic Chemicals, 3rd Ed.

Substance Name	Methyl 4-formylbenzoate
CAS No.	001571-08-0
Remarks for substance	Data are for structurally related substance terephthalic acid
Method/guideline	Measured
Year	1985
Log Pow	2.0
Data Qualities Reliabilities	Reliability code 3. Not reliable.
Remarks for Data Reliability	Code 3. Documentation insufficient for assessment.
References	Chan and Hansch, C. (1985) Pomona College Unpublished report.

Substance Name	Methyl 4-formylbenzoate
CAS No.	001571-08-0
Remarks for substance	Data are for structurally related substance dimethyl terephthalate
Method/guideline	Measured
Year	1995
Log Pow	2.25
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.

Remarks for Data Reliability	Code 2. Acceptable, well-documented publication/study report, which meets basic scientific principles.
References	Hansch C., Leo, A., and D. Hoekman (1995) Exploring QSAR - Hydrophobic, Electronic, and Steric Constants. Washington, DC: American Chemical Society; 69.

1.5 Water Solubility

Substance Name	Methyl 4-formylbenzoate
CAS No.	001571-08-0
Method/Guideline	Calculated
Value (mg/L) at Temperature	3136 mg/L at 25 °C
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Code 4. Calculated.
References	WSKOWWIN EPI Suite (2000) US Environmental Protection Agency.

Substance Name	Methyl 4-formylbenzoate
CAS No.	001571-08-0
Remarks for substance	Data are for structurally related substance terephthalic acid
Method/guideline	Measured
Value (mg/L) at Temperature	15 mg/L at 10 °C
Data Qualities Reliabilities	Reliability code 2. Reliable with restrictions.
Remarks for Data Reliability	Code 2. Acceptable, well-documented publication/study report, which meets basic scientific principles.
References	ICI Chemicals & Polymers Limited Product Safety Data: Pure Terephthalic Acid Jan. 1991.

Substance Name	Methyl 4-formylbenzoate
CAS No.	001571-08-0
Remarks for substance	Data are for structurally related substance terephthalic acid
Method/Guideline	Measured
Value (mg/L) at Temperature	19 mg/L at 25 °C
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Basic data given: comparable to guidelines/standards.
References	Bemis, Dindorf, Harwood, Samans. (1982) Kirk-Othmer Encyclopedia of Chemical Technology 3rd Ed Vol 17, 734.

Substance Name	Methyl 4-formylbenzoate
CAS No.	001571-08-0
Remarks for substance	Data are for structurally related substance dimethyl terephthalate
Value (mg/L) at Temperature	28.7 mg/L at 20 °C
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Acceptable, well-documented publication/study report, which meets basic scientific principles.
References	Montefibre Spa (undated) Unpublished report.

Substance Name	Methyl 4-formylbenzoate
CAS No.	001571-08-0
Remarks for substance	Data are for structurally related substance dimethyl terephthalate
Value (mg/L) at Temperature	19 mg/L at 25 °C
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Acceptable, well-documented publication/study report, which meets basic scientific principles.
References	Kuhne R. *et al*. (1995) Chemosphere, 30, 2061-77; HSDB No. 2580.

Substance Name	Methyl 4-formylbenzoate
CAS No.	001571-08-0

Remarks for substance	Data are for structurally related substance dimethyl terephthalate
Value (mg/L) at Temperature	37.2 mg/L at 25 °C
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Acceptable, well-documented publication/study report, which meets basic scientific principles.
References	Eastman Kodak Co. Environmental Safety Data Sheet; HAEL No. 77-0311 and 80-0056. Unpublished report.

2 ENVIRONMENTAL FATE AND PATHWAYS

2.1 Photodegradation

Substance Name	Methyl 4-formylbenzoate
CAS No.	001571-08-0
Method/guideline	Calculated
Test Type	AOPWIN
Halflife t1/2	7.371 hours
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Code 4. Calculated.
References	AOPWIN EPI Suite (2000) US Environmental Protection Agency.

Substance Name	Methyl 4-formylbenzoate
CAS No.	001571-08-0
Remarks for Substance	Data are for structurally related substance dimethyl terephthalate
Halflife t1/2	Approximately 3 days
Remarks for results	Substance was unreactive with ozone treatment.
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Basic data given: comparable to guidelines/standards.
References	Brown, S.L., Chan, F.Y., Jones, J.L., Liu, D.H. and McCaleb, K.E. (1975) Research program on hazard priority ranking of manufactured chemicals (chemicals 21-40). U.S. NTIS, PB-263162, p.195. Health and Environmental Effects Profile for Dimethyl Terephthalate (1984) EPA/600/X-84/152.

Substance Name	Methyl 4-formylbenzoate
CAS No.	001571-08-0
Remarks for Substance	Data are for structurally related substance dimethyl terephthalate
Halflife t1/2	4.7 to 46.6-days

Data Qualities Reliabilities	Reliability code 3. Not reliable.
Remarks for Data Reliability	Code 3. Documentation insufficient for assessment.
References	Howard, P.H., Boethling, R.S., Jarvis, W.F., Meylan, W.M., and Michalenko, E.M. editors, Handbook of Environmental Degradation Rates Lewis Publishers, p 465.

2.2 Stability in Water

Substance Name	Methyl 4-formylbenzoate
CAS No.	001571-08-0
Method/guideline	Measured/OECD Guideline 111
Test Type	Abiotic Degradation-Hydrolysis as Function of pH
GLP	Yes
Year	2003
Duration (days)	Up to 194 hours
Analytical procedures	GC(FID)
Remarks for Test Conditions	Test concentration was approximately 500 mg/L in 1% dimethylformamide for all experiments. In preliminary test hydrolysis was measured at 50 °C at pH=4,7, or 9. Based on preliminary test (greater than 10% hydrolysis after 120 hours), Test 1 was performed on pH=7 test solution. Based on results of Test 1 (not first order reaction kinetics), Test 2 was performed. Test 2 was performed at buffered pH=7 at 60, 70, and 80 C. Natural log of the test concentration 9mg/L) versus time (hours) was plotted. Linear regression analysis was performed to calculate observed reaction rate. As Arrhenius plot of log k versus 1/T was used to determine k(observed) and half life at 25 C.
Nominal	500 mg/L
Degradation %	In preliminary test, approximately 10% hydrolysis at 120-194 hours at pH=4, greater than 50% hydrolysis at 2.4 hours at pH=9, and greater than 10% hydrolysis at 120 hours at pH=7. In Test 1 at pH=7, reaction rate was determined to not be pseudo first order. In Test 2 at pH=7 and at 60, 70,and 80 °C hydrolysis data was generated to determine hydrolysis rate and half-life at 25 °C.

	half-life at 25 °C.
Halflife t1/2	The estimated half-life of the test substance was at pH=7 and 25 °C was 3286 hours. In the preliminary test at pH=9, the half-life was estimated to be less than 2.4 hours at 50 °C.
Breakdown products	4-formylbenzoic acid and methanol
Data Qualities Reliabilities	Reliability code 1. Reliable without restriction.
Remarks for Data Reliability	Code 1. Guideline study.
References	Hoffman C. (2003) Abiotic Degradation: Hydrolysis as a function of pH. Eastmen Chemical Company Report no. 1667-HYD. Unpublished report to Chemintox Inc.

Substance Name	Methyl 4-formylbenzoate
CAS No.	001571-08-0
Remarks for Substance	Data are for structurally related substance dimethyl terephthalate
Method/guideline	Measured
Halflife t1/2	1 to 4-weeks for surface water and 2 to 8-weeks for ground water.
Data Qualities Reliabilities	Reliability code 3. Not reliable.
Remarks for Data Reliability	Code 3. Documentation insufficient for assessment.
References	Howard P.H., Boethling, R.S., Jarvis, W.F., Meylan, W.M., and Michalenko, E.M. editors Handbook of Environmental Degradation Rates" Lewis Publishers, p 464.

Substance Name	Methyl 4-formylbenzoate
CAS No.	001571-08-0
Remarks for Substance	Data are for structurally related substance dimethyl terephthalate
Method/guideline	Measured
Halflife t1/2	321 days in neutral water at 25 °C
Data Qualities Reliabilities	Code 3. Documentation insufficient for assessment.
Remarks for Data Reliability	Code 3. Documentation insufficient for assessment.
References	Mabey W. and Mill, T. (1978) Critical review of hydrolysis of organic compounds in water under environmental conditions" J. Phys. Chem. Ref. Data. 7(2):383-415. Health and Environmental Effects Profile for Dimethyl Terephthalate (1984) EPA/600/X-84/152.

Substance Name	Methyl 4-formylbenzoate
CAS No.	001571-08-0
Remarks for Substance	Data are for structurally related substance dimethyl terephthalate
Method/guideline	Calculated
Halflife t1/2	23.9 days at pH=8 and 239 days at pH=7.
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Code 4. Calculated.
References	HYDROWIN EPI Suite (2000) US Environmental Protection Agency.

2.3 Biodegradation

Substance Name	Methyl 4-formylbenzoate
CAS No.	001571-08-0
Method	OECD Guide-line 301 B "Ready Biodegradability: Modified Sturm Test (CO_2 evolution)"
Innoculum	Domestic sewage, non-adapted
Total degradation	Greater than 60 % after 10 days
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Acceptable, well-documented publication/study report, which meets basic scientific principles.
Reference	Amoco Chemicals Co. (1992) Data cited in a letter with enclosures from Amoco Chemicals Co. to ICI Chemicals & Polymers Limited. Dated January 29, 1993.

Substance Name	Methyl 4-formylbenzoate
CAS No.	001571-08-0

Method	Calculated
Results	Probability of rapid biodegradation by the linear and non-linear model approaches or exceeds 1.
10 day window criteria	Yes
Conclusion remarks	Ultimate survey model predicts biodegradation of 2.99 weeks and primary survey model predicts in 4.03 days.
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Code 4. Calculated.
Reference	BIOWIN EPI Suite (2000) US Environmental Protection Agency.

Substance Name	Methyl 4-formylbenzoate
CAS No.	001571-08-0
Remarks for Substance	Data are for structurally related substance terephthalic acid
Method	OECD Guide-line 301 B "Ready Biodegradability: Modified Sturm Test
Year	1991
Contact time (units)	16 days
Innoculum	Activated sludge
Results	Readily biodegradable
Total degradation	16 days = 85.2% (10 mg/l) 82.6% (20 mg/l)
Data Qualities Reliabilities	Reliability code 1. Reliable without restriction.
Remarks for Data Reliability	Code 1. Guideline study.
Reference	Amoco Corporation (1991) Study on the ready biodegradability (Modified Sturm Test) of terephthalic acid. Conducted by Battelle Europe; Study # BE-EA-128-91-01-STT-03

Substance Name	Methyl 4-formylbenzoate
CAS No.	001571-08-0
Remarks for Substance	Data are for structurally related substance terephthalic acid
Method	OECD Guide-line 301 B "Ready Biodegradability: Modified Sturm Test (CO_2 evolution)"
Innoculum	Activated sludge
Total degradation	91 % after 28 days

Data Qualities Reliabilities	Reliability code 3. Not reliable.
Remarks for Data Reliability	Code 3. Documentation insufficient for assessment.
Reference	Gerike P. and Fischer WK. (1979) A correlation study of biodegradability determinations with various chemicals in various tests. Ecotox Environ Safety 3, 159-73.

Substance Name	Methyl 4-formylbenzoate
CAS No.	001571-08-0
Remarks for Substance	Data are for structurally related substance terephthalic acid
Test Type	Chemical oxygen demand
GLP	No
Year	1976
Contact time (units)	Up to 120 hours
Innoculum	From activated sludge
Remarks for Test Conditions	The concentration of test material is increased during activation until it reaches 200 mg/L COD. Degradation is carried out on an initial concentration equivalent to 200 mg/L COD and continues until there is no measured decrease in COD.
Degradation % After Time	99% at less than 120 hours
Results	Total degradation
Kinetic	119 mg COD/L
Time required for 10% degradation	Less than 120 hours
10 day window criteria	Yes
Total degradation	Yes
Conclusion remarks	Terephthalic acid is classified to be readily degradable.
Data Qualities Reliabilities	Reliability code 2. Reliable with restrictions.
Remarks for Data Reliability	Code 2. Acceptable, well-documented publication/study report, which meets basic scientific principles.
Reference	Pitter P. (1976) Determination of biological degradability of organic substrates. Water Research, 10, 231-235.

Substance Name	Methyl 4-formylbenzoate
CAS No.	001571-08-0
Remarks for Substance	Data are for structurally related substance methyl benzoate

Method	OECD Guideline 301B
Test Type	Sealed vessel test (CO2 production test)
Year	1995
Contact time (units)	28 days
Innoculum	10% by volume of secondary effluent from an unacclimatized activated sludge
Remarks for Test Conditions	The test concentration was nominal 10 mg/L organic carbon with a test temperature range of 17-22 C. The mean percentage biodegradation was calculated from 4 vessels on day 28
Degradation % After Time	95.3% at 28 days
10 day window criteria	Yes
Total degradation	Yes
Conclusion remarks	Methyl benzoate is classified as readily and ultimately biodegradable.
Data Qualities Reliabilities	Reliability code 1. Reliable without restriction.
Remarks for Data Reliability	Code 1. Guideline study.
Reference	Quest International Ltd. (1995) The biodegradability of methyl benzoate in the sealed vessel test. Unpublished report.

Substance Name	Methyl 4-formylbenzoate
CAS No.	001571-08-0
Remarks for Substance	Data are for structurally related substance methyl benzoate
Method	OECD Guideline 301B CO2 evolution test (Modified Sturm) and EPA's Ready Biodegradability: Modified Sturm Test
Test Type	Aerobic
GLP	Yes
Year	1995
Contact time (units)	28 days
Innoculum	Activated sludge (microbial content: 8.4 million CFU/mL) mixed liquor collected from the Downingtown Regional Water Pollution Control Center (Downingtown, PA)
Remarks for Test Conditions	In separate 4-L Erlenmeyer flasks containing 2 L modified biochemical oxygen demand water and supplied with CO2-free air, control (no methyl benzoate), glucose (20 mg/L0 and methyl benzoate (10 and 20 mg/L) were tested. Evolved CO2 was trapped in 3 bottles containing Ba(OH)2 and connected to each flask. Test substances were added by direct weight. During the study, the flasks were shaken at ~110 ppm and

	temperature ranged from 23-23.6 C. Airflow through rate was regulated to provide 1-2 bubbles/second into the CO2 traps. Trapped CO2 was precipitated as BaCO3 by reacting it with 0.024 N Ba(OH)2. To determine the amount of CO2 produced, the remaining Ba(OH)2 was titrated with 0.05 N standardized HCl. At the end of the study (28 days), concentrated H2SO4 was used to acidify the flasks' contents and after overnight aeration, the concentration of soluble organic carbon (SOC) was determined by final titration.
Degradation % After Time	Greater than 80% after 15 days
Results	Biodegradation was similar between both methyl benzoate concentrations and the glucose positive control (% SOC removed: 96.2, 100, and 99.3 for 20 mg glucose/L, 10 mg methyl benzoate/L, and 20 mg methyl benzoate/L, respectively). CO2 production by 10 days in the methyl benzoate flasks was approximately 80% and at the end of the study, the SOC content was approximately 1% at both concentrations.
10 day window criteria	Yes
Total degradation	Yes
Conclusion remarks	Methyl benzoate was considered readily biodegradable.
Data Qualities Reliabilities	Reliability code 1. Reliable without restriction.
Remarks for Data Reliability	Code 1. Guideline study.
Reference	Corby J. E. (1995) EPA: CO2 Production Test C-2000. Hoechst Celanese Corporation. Unpublished report.

Substance Name	Methyl 4-formylbenzoate
CAS No.	001571-08-0
Remarks for Substance	Data are for structurally related substance sodium benzoate
Method	OECD 301B Guideline CO2 evolution test - modified sealed vessel
Test Type	Aerobic
Year	1991
Contact time (units)	28 days
Innoculum	10% secondary effluent from sludge from local STP
Remarks for Test Conditions	2-10 mg DOC/L at 20 °C for 28 days; modification to OECD guidelines was the use of infra-red analyzers to measure CO2; 6 replicates
Degradation % After Time	85.7% at 21 days
Results	Mean biodegradation of 85.7% after 21 days (CI 82.4-89.2) and the authors concluded that the modification produced similar results to the standard protocol but was simpler and more

	results to the standard protocol but was simpler and more readily replicated. In addition, there was no practical difference between a concentration of 2 mg/L and 10 mg/L.
Time required for 10% degradation	1 day
10 day window criteria	Not reported
Total degradation	Yes
Conclusion remarks	Sodium benzoate was readily biodegradable.
Data Qualities Reliabilities	Reliability code 1. Reliable without restriction.
Remarks for Data Reliability	Code 1. Guideline study.
Reference	Birch R.R. and Fletcher, R.J. (1991) The application of dissolved inorganic carbon measurements to the study of aerobic biodegradability. Chemosphere, 23(4), 507-524.

Substance Name	Methyl 4-formylbenzoate
CAS No.	001571-08-0
Remarks for Substance	Data are for structurally related substance benzoic acid
Test Type	Chemical oxygen demand
GLP	No
Year	1976
Contact time (units)	Up to 120 hours
Innoculum	From activated sludge
Remarks for Test Conditions	The concentration of test material is increased during activation until it reaches 200 mg/L COD. Degradation is carried out on an initial concentration equivalent to 200 mg/L COD and continues until there is no measured decrease in COD.
Degradation % After Time	99% at less than 120 hours
Results	Total degradation
Kinetic	88.5 mg COD/L
Time required for 10% degradation	Less than 120 hours
10 day window criteria	Yes
Total degradation	Yes
Conclusion remarks	Material is readily degradable.
Data Qualities Reliabilities	Reliability code 2. Reliable with restrictions.

Remarks for Data Reliability	Code 2. Acceptable, well-documented publication/study report, which meets basic scientific principles.
Reference	Pitter P. (1976) Determination of biological degradability of organic substrates. Water Research, 10, 231-235.

2.4 Fugacity

Substance Name	Methyl 4-formylbenzoate
CAS No.	001571-08-0
Model Conditions	25 °C, 1000 lbs.
Test Type	Environmental Equilibrium Partitioning Model
Method	Mackay
Model Used	EQC V 2.11 Level I
Input Parameters	MW, log Kow, water solubility, MP & VP
Media	Air-Water Partition Coefficient
absorption coefficient	0.0000197
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Code 4. Calculated.
References	Trent University (1999) Level 1 Fugacity-based Environmental Equilibrium Partitioning Model Version 2.11. Based on Mackay, Donald (1991) Multimedia environmental models: The fugacity approach. Lewis Publications, CRC Press, Boca Raton, FL.

Substance Name	Methyl 4-formylbenzoate
CAS No.	001571-08-0
Model Conditions	25 °C, 1000 lbs.
Test Type	Environmental Equilibrium Partitioning Model
Method	Mackay
Model Used	EQC V 2.11 Level I

Input Parameters	MW, log Kow, water solubility, MP & VP
Media	Soil-Water Partition Coefficient
absorption coefficient	0.698
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Code 4. Calculated.
References	Trent University (1999) Level 1 Fugacity-based Environmental Equilibrium Partitioning Model Version 2.11. Based on Mackay, Donald (1991) Multimedia environmental models: The fugacity approach. Lewis Publications, CRC Press, Boca Raton, FL.

Substance Name	Methyl 4-formylbenzoate
CAS No.	001571-08-0
Model Conditions	25 °C, 1000 lbs.
Test Type	Environmental Equilibrium Partitioning Model
Method	Mackay
Model Used	EQC V 2.11 Level I
Input Parameters	MW, log Kow, water solubility, MP & VP
Media	Sediment-Water Partition Coefficient
absorption coefficient	1.40
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Code 4. Calculated.
References	Trent University (1999) Level 1 Fugacity-based Environmental Equilibrium Partitioning Model Version 2.11. Based on Mackay, Donald (1991) Multimedia environmental models: The fugacity approach. Lewis Publications, CRC Press, Boca Raton, FL.

Substance Name	Methyl 4-formylbenzoate
CAS No.	001571-08-0
Model Conditions	25 °C, 1000 lbs.
Test Type	Environmental Equilibrium Partitioning Model
Method	Mackay
Model Used	EQC V 2.11 Level I

Input Parameters	MW, log Kow, water solubility, MP & VP
Media	Suspended Sediment-Water Partition Coefficient
absorption coefficient	4.36
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Code 4. Calculated.
References	Trent University (1999) Level 1 Fugacity-based Environmental Equilibrium Partitioning Model Version 2.11. Based on Mackay, Donald (1991) Multimedia environmental models: The fugacity approach. Lewis Publications, CRC Press, Boca Raton, FL.

Substance Name	Methyl 4-formylbenzoate
CAS No.	001571-08-0
Model Conditions	25 °C, 1000 lbs.
Test Type	Environmental Equilibrium Partitioning Model
Method	Mackay
Model Used	EQC V 2.11 Level I
Input Parameters	MW, log Kow, water solubility, MP & VP
Media	Fish-Water Partition Coefficient
absorption coefficient	1.77
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Code 4. Calculated.
References	Trent University (1999) Level 1 Fugacity-based Environmental Equilibrium Partitioning Model Version 2.11. Based on Mackay, Donald (1991) Multimedia environmental models: The fugacity approach. Lewis Publications, CRC Press, Boca Raton, FL.

Substance Name	Methyl 4-formylbenzoate
CAS No.	001571-08-0
Model Conditions	25 °C, 1000 lbs.
Test Type	Environmental Equilibrium Partitioning Model
Method	Mackay
Model Used	EQC V 2.11 Level I

Input Parameters	MW, log Kow, water solubility, MP & VP
Media	Aerosol-Air Partition Coefficient
absorption coefficient	2,870,000
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Code 4. Calculated.
References	Trent University (1999) Level 1 Fugacity-based Environmental Equilibrium Partitioning Model Version 2.11. Based on Mackay, Donald (1991) Multimedia environmental models: The fugacity approach. Lewis Publications, CRC Press, Boca Raton, FL.

Substance Name	Methyl 4-formylbenzoate
CAS No.	001571-08-0
Model Conditions	25 °C, 1000 lbs.
Test Type	Environmental Equilibrium Partitioning Model
Method	Mackay
Model Used	EQC V 2.11 Level I
Input Parameters	MW, log Kow, water solubility, MP & VP
Media	Air
Estimated Distribution and Media Concentration	0.944%
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Code 4. Calculated.
References	Trent University (1999) Level 1 Fugacity-based Environmental Equilibrium Partitioning Model Version 2.11. Based on Mackay, Donald (1991) Multimedia environmental models: The fugacity approach. Lewis Publications, CRC Press, Boca Raton, FL.

Substance Name	Methyl 4-formylbenzoate
CAS No.	001571-08-0
Model Conditions	25 °C, 1000 lbs.
Test Type	Environmental Equilibrium Partitioning Model
Method	Mackay
Model Used	EQC V 2.11 Level I

Input Parameters	MW, log Kow, water solubility, MP & VP
Media	Water
Estimated Distribution and Media Concentration	95.97%
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Code 4. Calculated.
References	Trent University (1999) Level 1 Fugacity-based Environmental Equilibrium Partitioning Model Version 2.11. Based on Mackay, Donald (1991) Multimedia environmental models: The fugacity approach. Lewis Publications, CRC Press, Boca Raton, FL.

Substance Name	Methyl 4-formylbenzoate
CAS No.	001571-08-0
Model Conditions	25 °C, 1000 lbs.
Test Type	Environmental Equilibrium Partitioning Model
Method	Mackay
Model Used	EQC V 2.11 Level I
Input Parameters	MW, log Kow, water solubility, MP & VP
Media	Soil
Estimated Distribution and Media Concentration	3.0156%
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Code 4. Calculated.
References	Trent University (1999) Level 1 Fugacity-based Environmental Equilibrium Partitioning Model Version 2.11. Based on Mackay, Donald (1991) Multimedia environmental models: The fugacity approach. Lewis Publications, CRC Press, Boca Raton, FL.

Substance Name	Methyl 4-formylbenzoate
CAS No.	001571-08-0
Model Conditions	25 °C, 1000 lbs.
Test Type	Environmental Equilibrium Partitioning Model
Method	Mackay

Model Used	EQC V 2.11 Level I
Input Parameters	MW, log Kow, water solubility, MP & VP
Media	Sediment
Estimated Distribution and Media Concentration	0.067%
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Code 4. Calculated.
References	Trent University (1999) Level 1 Fugacity-based Environmental Equilibrium Partitioning Model Version 2.11. Based on Mackay, Donald (1991) Multimedia environmental models: The fugacity approach. Lewis Publications, CRC Press, Boca Raton, FL.

Substance Name	Methyl 4-formylbenzoate
CAS No.	001571-08-0
Model Conditions	25 °C, 1000 lbs.
Test Type	Environmental Equilibrium Partitioning Model
Method	Mackay
Model Used	EQC V 2.11 Level I
Input Parameters	MW, log Kow, water solubility, MP & VP
Media	Suspended Sediment
Estimated Distribution and Media Concentration	0.0021%
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Code 4. Calculated.
References	Trent University (1999) Level 1 Fugacity-based Environmental Equilibrium Partitioning Model Version 2.11. Based on Mackay, Donald (1991) Multimedia environmental models: The fugacity approach. Lewis Publications, CRC Press, Boca Raton, FL.

Substance Name	Methyl 4-formylbenzoate
CAS No.	001571-08-0
Model Conditions	25 °C, 1000 lbs.
Test Type	Environmental Equilibrium Partitioning Model

Method	Mackay
Model Used	EQC V 2.11 Level I
Input Parameters	MW, log Kow, water solubility, MP & VP
Media	Fish
Estimated Distribution and Media Concentration	0.00017%
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Code 4. Calculated.
References	Trent University (1999) Level 1 Fugacity-based Environmental Equilibrium Partitioning Model Version 2.11. Based on Mackay, Donald (1991) Multimedia environmental models: The fugacity approach. Lewis Publications, CRC Press, Boca Raton, FL.

Substance Name	Methyl 4-formylbenzoate
CAS No.	001571-08-0
Model Conditions	25 °C, 1000 lbs.
Test Type	Environmental Equilibrium Partitioning Model
Method	Mackay
Model Used	EQC V 2.11 Level I
Input Parameters	MW, log Kow, water solubility, MP & VP
Media	Aerosol
Estimated Distribution and Media Concentration	0.0000542%
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Code 4. Calculated.
References	Trent University (1999) Level 1 Fugacity-based Environmental Equilibrium Partitioning Model Version 2.11. Based on Mackay, Donald (1991) Multimedia environmental models: The fugacity approach. Lewis Publications, CRC Press, Boca Raton, FL.

3 ECOTOXICITY

3.1 Acute Toxicity to Fish

Substance Name	Methyl 4-formylbenzoate
CAS No.	001571-08-0
Method/guideline	Calculated
Species/Strain/Supplier	Fish
Exposure Period	96 hours
Conclusion remarks	The 96 hour LC50 was 19.0 mg/L.
Remarks for Test Conditions	Based on aldehyde ECOSAR Class, 96 hour LC50 was calculated to be 19 mg/L. Based on ester ECOSAR Class, 96 hour LC50 was calculated to be 43 mg/L
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Code 4. Calculated.
Reference	ECOSAR EPI Suite (2000) US Environmental Protection Agency.

Substance Name	Methyl 4-formylbenzoate
CAS No.	001571-08-0
Remarks for Substance	Data are for structurally related substance terephthalic acid
Method/guideline	OECD Guideline 203 "Fish, Acute Toxicity Test"
GLP	Yes
Year	1991
Species/Strain/Supplier	Golden orfe (*Leuciscus idus melanotus*)
Exposure Period	96 hours
Remarks for Test Conditions	Fish were held for 21 days in a 376 liter glass vessels containing 327 liters of reconstituted water (19 °C, 85-95% oxygen). Fish density was 0.51 g/liter. They were fed five times a week with 50% Tetra Special Mix and 50% IBL Novo food tablets prior to study. The study was conducted in 16 liter stainless steel vessels that contained 10 liters of test solution. Test solution was not renewed. At the time of the test, fish were an average of 4.86 ± 0.47 cm in length and weighed 1.028 ± 0.246 g. Ten fish were placed in each vessel (for a loading rate of 1.028 g/l). Fish were not fed during the test. The test article

	of 1.028 g/l). Fish were not fed during the test. The test article was diluted with reconstituted purified water to yield nominal concentrations of 130, 220, 350, 600 and 1000 ppm. The actual concentration of the highest exposure level was 999.3 ppm at time 0, and 922.2 ppm at 96 hours. Fish were maintained at 22.0 ± 0.07 °C, a pH of 7.57 ± 0.26, conductivity of 1026.9 ± 367.74 microS/cm, alkalinity of 41.68 ± 1.14 mg/l CaCO3, hardness of 193.86 ± 75.0 mg/l CaCO3, and a light/dark photoperiod of 16/8 hours. The dissolved oxygen content was 8.33 ± 0.22 mg/l and was maintained through aeration. Parameters were determined at time 0 and every 24 hours thereafter. Under the test conditions it was believed that some of the terephthalic acid was converted to a salt form. Fish loading was slightly above the 1.0 g/l recommended level, but was not believed to impact the results.
Remarks for results	Dissolved oxygen, temperature, conductivity, alkalinity, and hardness did not vary between groups. The pH of the water decreased slightly as a function of time and increasing concentration of test material (i.e. the pH of the vessel containing 1000 mg/l at 96 hours was 7). All test condition values were within acceptable limits. No mortalities or behavioral changes were noted at any concentration during the study.
Data Qualities Reliabilities	Reliability code 1. Reliable without restriction.
Remarks for Data Reliability	Code 1. Guideline study.
Reference	Amoco Corporation (1993a) A Study of the Acute Toxicity to Fish (*Leuciscus idus melanotus*) of Terephthalic Acid. Conducted by Battelle Europe; Study # BE-EA-128-91-01-F3A-3; Reference no. 21

Substance Name	Methyl 4-formylbenzoate
CAS No.	001571-08-0
Remarks for Substance	Data are for structurally related substance terephthalic acid
Method/guideline	OECD Guideline 203 "Fish, Acute Toxicity Test
Test Type	Semistatic
GLP	Yes
Year	1991
Species/Strain/Supplier	*Salmo gairdneri*
Exposure Period	96 hours
Remarks for Test Conditions	LC0 - 500 mg/L; LC50 - 798-1640 mg/L; LC100 - 1500 mg/L. Mean value 1157 mg/L.
Conclusion remarks	The LC50 was 798 - 1640 mg/L.

Data Qualities Reliabilities	Reliability code 1. Reliable without restriction.
Remarks for Data Reliability	Code 1. Guideline study.
Reference	ICI Chemicals & Polymers Ltd. (1991) Internal report, BLS 1200/B.

Substance Name	Methyl 4-formylbenzoate
CAS No.	001571-08-0
Remarks for Substance	Data are for structurally related substance dimethyl terephthalate
Test Type	Static test
Species/Strain/Supplier	Minnow/flathead
Exposure Period	96 hours
Remarks for Test Conditions	100% mortality at 30 mg/L
Conclusion remarks	LC50 = 9.6 mg/L, NOEC = 3 mg/kg.
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Acceptable, well-documented publication/study report, which meets basic scientific principles.
Reference	Eastman Kodak Co. (1984) Unpublished data.

Substance Name	Methyl 4-formylbenzoate
CAS No.	001571-08-0
Remarks for Substance	Data are for structurally related substance dimethyl terephthalate
Test Type	Static test
Species/Strain/Supplier	Minnow/flathead
Exposure Period	96 hours
Conclusion remarks	LC50 = 45 mg/L
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Acceptable, well-documented publication/study report, which meets basic scientific principles.
Reference	Eastman Kodak Co. (1984) Unpublished data.

Substance Name	Methyl 4-formylbenzoate

CAS No.	001571-08-0
Remarks for Substance	Data are for structurally related substance methyl benzoate
Method/guideline	TSCA Environmental Effects Testing Guideline 797.1400
Test Type	Acute Fish Toxicity
GLP	Yes
Year	1997
Species/Strain/Supplier	Bluegill sunfish (*Lepomis macrochirus*)
Exposure Period	96 hours
Analytical monitoring	
Remarks for Test Conditions	Groups of 10 juvenile bluegill fish (average length 22 mm and weight 0.19 g) from Northeastern Biologists (Rhinebeck, NY) were exposed to solvent control (acetone), 5.0, 10, 20, 40 or 80 mg methyl benzoate/L for 96 hours in 10 L glass tanks containing 9 L of test media (methyl benzoate dissolved in acetone and diluted with reconstituted water). The reconstituted freshwater had an initial hardness of 80 mg/L (as CaCO3) and alkalinity of 11. Each test was conducted in duplicate. Oxygen content, and pH were measured at the beginning of the test and at 24, 48, 72, and 96 hours. Test temperatures ranged from 20.3 to 23.9 C. Fish were observed for signs of toxicity every 24 hours.
Observations on precipitation	Undissolved test substance was noted at the 2 highest concentrations.
Nominal concentrations as mg/L	5.0, 10, 20, 40 or 80 mg/L
Remarks fields for results	No deaths occurred in controls and at concentrations up to and including 10 mg/L. Mortality was 100% at the highest concentration. Loss of equilibrium was reported in fish exposed to 20 mg/L or higher and dose-related pigmentation darkening was seen in all treatment groups. Undissolved test substance was noted at the 2 highest concentrations.
Conclusion remarks	The 96 hour LC50 was 28.3 mg/L and the NOEC was 10 mg/L based on mortality and loss of equilibrium. The NOEC for color change was not determined but was expected to be less than 5.0 mg/L.
Data Qualities Reliabilities	Reliability code 1. Reliable without restriction.
Remarks for Data Reliability	Code 1. Guideline study.
Reference	Cunningham F.J. (1997a) C-2000 (Methyl benzoate) Acute toxicity to Bluegill, *Lepomis macrochirus*, under static conditions. Project No. J9605001a. Private communication to FFHPVC. Unpublished report.

Substance Name	Methyl 4-formylbenzoate
CAS No.	001571-08-0
Remarks for Substance	Data are for structurally related substance methyl benzoate
Method/guideline	Calculated
Species/Strain/Supplier	Fish
Exposure Period	96 hour
Conclusion remarks	The 96 hour LC50 was 18.0 mg/L.
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Code 4. Calculated.
Reference	ECOSAR EP Suite (2000) US Environmental Protection Agency.

Substance Name	Methyl 4-formylbenzoate
CAS No.	001571-08-0
Remarks for Substance	Data are for structurally related substance benzaldehyde
Method/guideline	Experimental
Test Type	Larval survival and growth test
GLP	Yes
Year	1996
Species/Strain/Supplier	Fathead minnow *(Pimephales promelas*)
Exposure Period	1, 4, and 7 days
Analytical monitoring	HPLC with an ultraviolet detector at 254 um
Nominal concentrations as mg/L	1st test: 0.9, 1.8, 3.6, 7.2, 14.3; 2nd test: 0.11, 0.22, 0.45, 0.9, 1.8, 3.6, 7.2
Measured concentrations as mg/L	Not detectable at 2 lowest concentrations, 0.02, 0.13, 0.20 for 3 highest concentrations.
Remarks for Test Conditions	Each test concentration had 4 replicates with 10 larvae each. Larvae were fed once on the 1st day and 2x/day on days 1-6. Dead and surviving larvae were counted and survivors were prepared for dry weight determination.
Remarks for results	The NOEC for growth of 7-d larvae was 1.8 mg/L. The NOEC for 1- and 4- day larvae was less than 0.9 mg/L. NOEC for survival of 1- and 4-d larvae was 3.6 mg/L (first test). NOEC for survival in second test was 0.22 mg/L for 1-d larvae and 1.8 mg/L for 4- and 7-d.
Conclusion remarks	1-d larvae more sensitive than older larvae to benzaldehyde.

Data Qualities Reliabilities	Reliability code 1. Reliable without restriction.
Remarks for Data Reliability	Code 1. Guideline study.
Reference	Pickering Q. H., Lazorchak, J. M. and Winks. K. L. (1996) Subchronic sensitivity of one-, four-, and seven-day-old-fathead minnow (Pimephales promelas) larvae to five toxicants. Environmental Toxicology and Chemistry, 15(3), 353-359.

Substance Name	Methyl 4-formylbenzoate
CAS No.	001571-08-0
Remarks for Substance	Data are for structurally related substance benzaldehyde
Method/guideline	Experimental
Species/Strain/Supplier	Guppy (*Poecilia reticulata*)
Exposure Period	14 days
Analytical monitoring	Tracor 550 gas chromatograph
Remarks for Test Conditions	Experiments were conducted under semi-static conditions with daily renewal of test solutions. A minimum of 5 concentrations of benzaldehyde were tested. The guppies were acclimated for 12 days prior to testing and 10 guppies/concentration were tested. The control group consisted of 12 guppies exposed to the test substance carrier solvent, acetone. Logit transformation was used to calculate the LC50.
Measured concentrations as mg/L	Not reported
Conclusion remarks	The 14-day LC50 for benzaldehyde was reported to be 1.57 umoles/L. The log P was calculated to be 1.49 (Rekker, 1977).
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Acceptable, well-documented publication/study report, which meets basic scientific principles.
Reference	Deneer J.W., Seinen, W., and Hermens, J.L.M. (1988) The acute toxicity of aldehydes to the guppy. Aquatic Toxicol., 12, 185-192.

Substance Name	Methyl 4-formylbenzoate
CAS No.	001571-08-0
Remarks for Substance	Data are for structurally related substance benzaldehyde
Method/guideline	Calculated
Species/Strain/Supplier	Fish
Exposure Period	96 hour

Conclusion remarks	The 96 hour LC50 was 13.0 mg/L.
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Code 4. Calculated.
Reference	ECOSAR EP Suite (2000) US Environmental Protection Agency.

3.2 Acute Toxicity to Aquatic Invertebrates

Substance Name	Methyl 4-formylbenzoate
CAS No.	001571-08-0
Method/guideline	Calculated
Species/Strain/Supplier	*Daphnia magna*
Conclusion remarks	The 48-hour LC50 was 16.4 mg/L.
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Data Reliability Remarks	Code 4. Calculated.
Reference	ECOSAR EPI Suite (2000) US Environmental Protection Agency.

Substance Name	Methyl 4-formylbenzoate
CAS No.	001571-08-0
Remarks for Substance	Data are for structurally related substance terephthalic acid
Method/guideline	OECD Guideline 202
Test Type	Static test
GLP	Yes
Year	1991

Species/Strain/Supplier	*Daphnia magna*
Test Details	48 hours
Remarks for Test Conditions	Adult Daphnia (approx. 20/vessel) were kept in 3.5 liter vessels containing 2 liters of Elendt M 7 medium (22 °C) and were fed with algae. Daphnia were placed in reconstituted water 24 hours prior to test. New-born *Daphids* were collected and held for 6 hours. The study was conducted in quadruplicate using 5 new-born Daphnia (6-20 hours)/concentration in each 300 ml test vessel. The test article was diluted with purified reconstituted water to yield nominal concentrations of 0, 80, 130, 220, 350, 600 and 1000 ppm in a total volume of 200 ml. The actual concentration of the highest exposure level was 951.5 ppm at time 0, and 982 ppm at 48 hours. A group of Daphnids was also exposed to water that contained 1.57 g NaOH that was pH adjusted by adding HCl (salinity control). Vessels were not aerated. Daphnia were maintained at 22.07 ± 0.11 °C, a pH of 7.79 ± 0.06, dissolved oxygen content of 8.31 ± 0.15 mg/l, conductivity of 929.38 ± 369.64 microS/cm, alkalinity of 42.91 ± 1.55 mg/l CaCO3, hardness of 232.64 ± 12.61 mg/l CaCO3, and a light/dark photoperiod of 16/8 hours. The number of immobilized fleas was noted at 0, 24 and 48 hours. Under the test conditions it was believed that some of the terephthalic acid was converted to a salt. Immobilization at the highest dose was only noted in 1 of the 20 fleas.
Remarks for results	Water quality parameters of pH, oxygen concentration, temperature and alkalinity remained within acceptable limits throughout the study and did not differ significantly with time or increasing concentration of test material. Conductivity of the saline control group (1660 at time 0) was higher than most other groups. Conductivity increased with increasing concentration of test material (from 570 to 1230 microS/cm at time 0 for 1000 ppm). Lethality was 1/20 (5%) in the salinity control group and 1/20 in *Dahpnia* exposed to 1000 ppm
Conclusion remarks	The NOEC = 600 mg/L (nominal); EC0 = 600 mg/L (nominal); EC50 = greater than 1000 (nominal)
Data Qualities Reliabilities	Reliability code 1. Reliable without restriction.
Data Reliability Remarks	Code 1. Guideline study.
Reference	Amoco Corporation (1993b) A study of the acute immobilization to *daphnia* of terephthalic acid. Conducted by Battelle Europe; Study # BE-EA-128-91-02-DAK-3.

Substance Name	Methyl 4-formylbenzoate
CAS No.	001571-08-0
Remarks for Substance	Data are for structurally related substance dimethyl terephthalate
Test Type	Static test

Species/Strain/Supplier	*Daphnia magna*
Test Details	96 hour
Conclusion remarks	The LC50 = to or greater than 100 mg/L
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Data Reliability Remarks	Code 2. Acceptable, well-documented publication/study report, which meets basic scientific principles.
Reference	Eastman Kodak Co. (1977) Unpublished report.

Substance Name	Methyl 4-formylbenzoate
CAS No.	001571-08-0
Remarks for Substance	Data are for structurally related substance dimethyl terephthalate
Test Type	Static test
Species/Strain/Supplier	*Dugesia tigrina* (Flatworm)
Test Details	96 hour
Conclusion remarks	The LC50 = to or greater than 100 mg/L
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Data Reliability Remarks	Code 2. Acceptable, well-documented publication/study report, which meets basic scientific principles.
Reference	Eastman Kodak Co. (1977) Unpublished report.

Substance Name	Methyl 4-formylbenzoate
CAS No.	001571-08-0
Remarks for Substance	Data are for structurally related substance dimethyl terephthalate
Test Type	Static test
Species/Strain/Supplier	*Helisoma trivolvis* (Snail)
Conclusion remarks	The LC50 = to or greater than 100 mg/L
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Data Reliability Remarks	Code 2. Acceptable, well-documented publication/study report, which meets basic scientific principles.
Reference	Eastman Kodak Co. (1977) Unpublished report.

Substance Name	Methyl 4-formylbenzoate
CAS No.	001571-08-0
Remarks for Substance	Data is for structurally related substance dimethyl terephthalate
Test Type	Static test
Species/Strain/Supplier	*Helisoma trivolvis* (Snail)
Test Details	96 hour
Conclusion remarks	The LC50 = to or greater than 30 mg/L and NOEC 3 mg/L.
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Data Reliability Remarks	Code 2. Acceptable, well-documented publication/study report, which meets basic scientific principles.
Reference	Eastman Kodak Co. (1984) Unpublished data.

Substance Name	Methyl 4-formylbenzoate
CAS No.	001571-08-0
Remarks for Substance	Data is for structurally related substance dimethyl terephthalate
Test Type	Static Test
Species/Strain/Supplier	*Daphnia magna*
Test Details	48 hours
EC50, EL50, LC0, at 24,48 hours	EC50 = to or greater than 30 mg/L
Conclusion remarks	Exposure to 30 mg/L induced 40% immobility
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Data Reliability Remarks	Code 2. Acceptable, well-documented publication/study report, which meets basic scientific principles.
Reference	Eastman Kodak Co. (1984) Unpublished report.

Substance Name	Methyl 4-formylbenzoate
CAS No.	001571-08-0
Remarks for Substance	Data is for structurally related substance dimethyl terephthalate
Species/Strain/Supplier	*Daphnia magna*
Test Details	48 hours
EC50, EL50, LC0, at 24,48 hours	LC50 = 30.4 mg/L

hours	
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Data Reliability Remarks	Code 2. Acceptable, well-documented publication/study report, which meets basic scientific principles.
Reference	DuPont Chemicals; Material Safety Data Sheet.

Substance Name	Methyl 4-formylbenzoate
CAS No.	001571-08-0
Remarks for Substance	Data are for structurally related substance methyl benzoate
Method/guideline	Experimental
Test Type	Static freshwater toxicity test
GLP	Yes
Year	1996
Species/Strain/Supplier	*Daphnia magna*
Test Details	Ten *Daphnia magna* were added in pairs to 300 mL glass test chambers containing methyl benzoate dissolved in acetone and diluted with freshwater to a volume of 250 mL. The test concentrations were 9.38, 18.8, 37.5, 75, 150, and 300 mg/L. *Daphnia* were exposed for 48 hours. Freshwater and solvent controls were also tested. Treatments were performed in duplicate. Survival and water temperature were monitored daily; whereas pH and dissolved oxygen concentrations were measured at the beginning and end of the test.
Nominal concentrations as mg/L	9.38, 18.8, 37.5, 75, 150, and 300 mg/L
EC50, EL50, LC0, at 24,48 hours	48 hour EC50 = 32.1 mg/L
Biological observations	No deaths in controls and exposures up to and including 18.8 mg/L. At higher exposures, approximately 75% of the *Daphnia* were dead or immobilized. Also at these higher concentrations, undissolved methyl benzoate was initially reported, but was no longer observed at 24 hours.
Conclusion remarks	The 48-hour EC50 for methyl benzoate in *Daphnia* was 32.1 mg/L and the no-observed-effect concentration was 18.8 mg/L.
Data Qualities Reliabilities	Reliability code 1. Reliable without restrictions.
Data Reliability Remarks	Code 1. Comparable to guideline study.
Reference	Cunningham F.P. (1997b) C-2000 (Methyl Benzoate): Acute toxicity to the water flea, Daphnia magna, under static conditions. Project No. J9605001b. Unpublished report.

Substance Name	Methyl 4-formylbenzoate
CAS No.	001571-08-0
Remarks for Substance	Data are for structurally related substance methyl benzoate
Method/guideline	Calculated
Species/Strain/Supplier	*Daphnia magna*
Conclusion remarks	48 hour LC50 = 84.0 mg/L
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Data Reliability Remarks	Code 4. Calculated.
Reference	ECOSAR EPI Suite (2000) US Environmental Protection Agency.

Substance Name	Methyl 4-formylbenzoate
CAS No.	001571-08-0
Remarks for Substance	Data are for structurally related substance benzaldehyde
Method/guideline	Experimental
Test Type	24 hour LC50
GLP	No
Year	1977
Species/Strain/Supplier	*Daphnia magna*
Test Details	*Daphnia magna* (30/group, 24 hours old) were maintained in chlorine free tap water saturated with oxygen, pH of 7.7-7.7 and temperature of 20-22 C. The LC50, LC0 and LC100 were determined.
EC50, EL50, LC0, at 24,48 hours	24 hour LC50 = 50, LC0 = 6.3 and LC100 = 100 mg/L
Conclusion remarks	LC50 = 50 mg/L; LC0 = 6.3 mg/L; LC100 = 100 mg/L
Data Qualities Reliabilities	Reliability code 2. Reliable with restrictions.
Data Reliability Remarks	Code 2. Acceptable, well-documented publication/study report, which meets basic scientific principles.
Reference	Bringmann G. and Kuehn, R. (1977) Befunde der Schadwirkung wassergefaehrdender Stoffe gegen Daphnia magna. [Results of the damaging effects of water pollutants on Daphnia magna.] A Wasser Abwasser Forsch., 10(5, :161-166.

Substance Name	Methyl 4-formylbenzoate

CAS No.	001571-08-0
Remarks for Substance	Data are for structurally related substance benzaldehyde
Method/guideline	Calculated
Species/Strain/Supplier	*Daphnia magna*
Conclusion remarks	48 hour LC50 = 12.0 mg/L
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Data Reliability Remarks	Code 4. Calculated.
Reference	ECOSAR EPI Suite (2000) US Environmental Protection Agency.

3.3 Acute Toxicity to Aquatic Plants

Substance Name	Methyl 4-formylbenzoate
CAS No.	001571-08-0
Method/guideline	Calculated
Species/Strain/Supplier	Green algae
Exposure Period	96 hour
Conclusion remarks	The EC50 = 204 mg/L
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Code 4. Calculated.
Reference	ECOSAR EPI Suite (2000) US Environmental Protection Agency.

Substance Name	Methyl 4-formylbenzoate
CAS No.	001571-08-0
Remarks for Substance	Data are structurally related substance terephthalic acid
Method/guideline	OECD Guideline 201

Test Type	Static test
Year	1991-1992
Species/Strain/Supplier	Green algae
Exposure Period	96 hour
Remarks for Test Conditions	The study was conducted in quadruplicate using 104 cells/ml per test concentration. A total of 100 ml of test solution was used. The age of the stock and pre-cultures were 13 and 4 days, respectively. Test vessels consisted of 300 ml Erlenmeyer flasks containing 100 ml of test solution and were capped with a cotton plug. Flasks were shaken at a rate of 80 oscillations/minute. Room temperature was 23 ± 1 °C, pH ranged from 8.1- 10.2, and a light/dark photoperiod of 24/0 hours was used. The quantum flux density was 120uE/sec-m-2. Nominal test concentrations were 62.5, 125, 250, 500 and 1000 ppm. The actual concentration of the highest exposure level was 927.05 ppm at time 0 and 408.85 ppm at 96 hours. Lower concentrations were within 70-105% nominal levels at time 0, but less than 10 ppm after 96 hours. Growth inhibition was determined daily by counting the number of cells per volume of test solution (cell concentration). Under the test conditions it was believed that some of the terephthalic acid was converted to a salt. The decrease in concentration was believed to be due to adsorption of the material by the algae. Cells in all replicates treated with 125 – 1000 ppm were noted to have appeared paler than controls or those treated with 62.5 ppm between 48-72 hours.
NOEC, LOEC or NOEL, LOEL	NOEC is greater than 1000 (nominal); EC50 is greater than 1000 (nominal)
Remarks for results	The pH and temperature of flasks containing test material remained within acceptable limits throughout the study and did not vary with time or concentration of test material. The pH of the control medium increased from 8.2 to 10.2. There was no effect of test material on algal growth. The test was considered valid, as the concentration of control algae increased by a factor of 93.3 within 3 days (at least a factor of 16 is required).
Data Qualities Reliabilities	Reliability code 1. Reliable without restriction.
Remarks for Data Reliability	Code 1. Guideline study.
Reference	Amoco Corporation (1993c) A study of the toxicity to algae (Scenedesmus subspicatus) of terephthalic acid. Conducted by Battelle Europe; Study # BE-EA-128-91-02-ALG-3.

Substance Name	Methyl 4-formylbenzoate
CAS No.	001571-08-0
Remarks for Substance	Data are for structurally related substance dimethyl terephthalate

Method/guideline	Directive 88/302 EEC
Species/Strain/Supplier	Green algae
Exposure Period	72 hour
NOEC, LOEC or NOEL, LOEL	EC50 greater than 32.3 mg/L; NOEC = 10.8 mg/L
Remarks for results	No analytical monitoring, concentrations were nominal. For the growth rate endpoint, an EC50 was not reached at the highest concentration tested (32.3 mg/L). At test beginning pH was 7.7-8.0 and it was 8.2-9.1 at conclusion. The estimated algal toxicity EC50 using ECOTOX software is 1.5 mg/L (96-hr).
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Acceptable, well-documented publication/study report, which meets basic scientific principles.
Reference	Huls AG (1993) Report AW-301. Unpublished data.

Substance Name	Methyl 4-formylbenzoate
CAS No.	001571-08-0
Remarks for Substance	Data are for structurally related substance methyl benzoate
Method/guideline	Calculated
Species/Strain/Supplier	Green algae
Conclusion remarks	The 96 hour EC50 = 1.4 mg/L
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Code 4. Calculated.
Reference	ECOSAR EPI Suite (2000) US Environmental Protection Agency

Substance Name	Methyl 4-formylbenzoate
CAS No.	001571-08-0
Remarks for Substance	Data are for structurally related substance benzaldehyde
Method/guideline	Respiration of photosynthesizing cells
GLP	No
Year	1971
Species/Strain/Supplier	*Chlorella vulgaris*
Endpoint basis	Stimulation of cell respiration (oxygen uptake)

Exposure Period	5 hours
Analytical monitoring	Warburg respirometer
Remarks for Test Conditions	Cells were maintained in the dark at 25 °C in 20 ml flasks and oxygen uptake was measured over a period of 5 hours at a pH of 5.6 or pH of 7.2.
Nominal concentrations as mg/L	0.00005, 0.0001, and 0.001 M
Biological observations	Stimulation of respiration of 0, 10, and 90% at pH 5.6 and 5, 50, and 60% at pH 7.2 at 0.00005, 0.0001, and 0.001 M, respectively.
Control response satisfactory?	Unknown
Appropriate statistical evaluations?	None reported
Conclusion remarks	In a dose-dependent manner, benzaldehyde stimulated the respiration of cells from Chlorella vulgaris.
Data Qualities Reliabilities	Reliability code 2. Reliable with restrictions.
Remarks for Data Reliability	Code 2. Acceptable, well-documented publication/study report, which meets basic scientific principles.
Reference	Dedonder A. and Van Sumere, C.F. (1971) The effect of phenolics and related compounds on the growth and the respiration of Chlorella vulgaris. Z Pflanzenphysiol Bd., 65, 70-80.

Substance Name	Methyl 4-formylbenzoate
CAS No.	001571-08-0
Remarks for Substance	Data are for structurally related substance benzaldehyde
Method/guideline	Growth and cell division
GLP	No
Year	1971
Species/Strain/Supplier	*Chlorella vulgaris*
Endpoint basis	Inhibition of cell growth
Exposure Period	80 and 160 hours
Remarks for Test Conditions	Cell growth was determined by direct cell counting using a Burker counting chamber.
Nominal concentrations as mg/L	0.00005, 0.0001, and 0.001 M
Biological observations	Growth inhibition of 30, 30 and 95% after 80 hours and 7, 10 and 90% after 160 hours at 0.00005, 0.0001, and 0.001 M (8.5, 17, and 170 mg/L), respectively.

Control response satisfactory?	Unknown
Appropriate statistical evaluations?	None reported
Conclusion remarks	In a dose-dependent manner, benzaldehyde inhibited growth of Chlorella vulgaris.
Data Qualities Reliabilities	Reliability code 2. Reliable with restrictions.
Remarks for Data Reliability	Code 2. Acceptable, well-documented publication/study report, which meets basic scientific principles.
Reference	Dedonder A. and Van Sumere, C.F. (1971) The effect of phenolics and related compounds on the growth and the respiration of Chlorella vulgaris. Z Pflanzenphysiol Bd., 65, 70-80.

Substance Name	Methyl 4-formylbenzoate
CAS No.	001571-08-0
Remarks for Substance	Data are for structurally related substance benzaldehyde
Method/guideline	Calculated
Species/Strain/Supplier	Green algae
Exposure Period	96 hour
Conclusion remarks	The 96 hour EC50 = 152.0 mg/L
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Code 4. Calculated.
Reference	ECOSAR EPI Suite (2000) US Environmental Protection Agency

4 HUMAN HEALTH TOXICITY

4.1 Acute Toxicity

Substance Name	Methyl 4-formylbenzoate
CAS No.	001571-08-0
Remarks for Substance	Data are for structurally related substance terephthalic acid
Method/guideline	Oral LD50
Test Type	Acute oral toxicity
GLP	Yes
Year	1990
Species/strain	Rat/Sprague-Dawley
Sex	Male and Female
# of animals per sex per dose	5/sex
Vehicle	Water
Route of Administration	Oral
Remarks for Test Conditions	A single dose of 5000 mg/kg test material (diluted with water to form a 50% w/v suspension) was administered by oral gavage at a rate of 10 ml/kg. At initiation of dosing rats were approximately 9 weeks of age and weighed an average of 310 g (M) and 183 g (F). Body weights were assessed at dosing, and on Days 7 and 14. Animals were observed daily for 14 days at which time they were killed and necropsied
Value LD50 or LC50 with confidence limits	LD50 = greater than 5,000 mg/kg bw
Remarks for Results	No deaths were noted in either sex. Clinical signs consisted of diarrhea (M 5/5; F 5/5), redness around nose (M 3/5; F 2/5), and discolored inguinal fur (M 4/5; F 1/5). Signs diminished in most animals by 48 hours and all were normal at study termination. Mean body weights increased during the study. No alterations were noted during gross necropsy.
Data Qualities Reliabilities	Reliability code 1. Reliable without restriction.
Remarks for Data Reliability	Code 1. Comparable to guideline study.
References	Amoco Corporation (1990) Acute oral toxicity study of terephthalic acid in rats. Conducted by IIT Research Institute. IITRI Study #1557.

Substance Name	Methyl 4-formylbenzoate
CAS No.	001571-08-0
Remarks for Substance	Data are for structurally related substance dimethyl terephthalate
Method/guideline	Oral LD50
Test Type	Acute oral toxicity
GLP	No
Year	1973
Species/strain	Rat/Long-Evans Hooded
Sex	Male and Female
# of animals per sex per dose	3-6/sex
Vehicle	None
Route of Administration	Oral
Remarks for Test Conditions	Oral doses of 0, 3000, 3900, 5020 or 6590 mg/kg DMT were administered to groups of 3-6 male rats as a 20% solution in corn oil. The animals were observed for clinical signs of toxicity and mortality for 14-days. After 14-days of observations, the animals were euthanized, autopsied, and examined for gross pathology and histopathology.
Value LD50 or LC50 with confidence limits	LD50 = to or greater than 6590 mg/kg bw
Number of deaths at each dose level	None
Remarks for Results	No mortality was observed during the 14-day post-treatment period. Clinical signs of toxicity were limited to slight to moderate weakness at all dose levels and slight tremors and ataxia at the 5,020 and 6,590 mg/Kg dose levels. No signs of gross or histopathological changes due to systemic toxicity were noted at necropsy.
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Acceptable, well-documented publication/study report, which meets basic scientific principles.
References	Krasavage, W.J., Yanno, F.J., and Terhaar, C.J. (1973) "Dimethyl terephthalate (DMT): Acute Toxicity, Subacute Feeding and Inhalation Studies in Male Rats." J. Amer. Ind. Hyg. Assoc., 34(10):455-462

Substance Name	Methyl 4-formylbenzoate

CAS No.	001571-08-0
Remarks for Substance	Data are for structurally related substance benzaldehyde
Method/guideline	Oral LD50
Test Type	Acute oral toxicity
GLP	No
Year	1967
Species/strain	Rat/white
Sex	Not reported
# of animals per sex per dose	Not reported
Vehicle	Not reported
Route of Administration	Oral
Remarks for Test Conditions	Total of 70 rats orally administered benzaldehyde and observed for 7 days.
Value LD50 or LC50 with confidence limits	LD50 = 2850 mg/kg bw (no confidence limits reported)
Number of deaths at each dose level	Not reported
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Code 4. Only short abstract available.
References	Sporn A., Dinu, I., and Stanclu, V. (1967) Cercetari cu privire la toxicitatea aldehidei benzoice. [Research regarding the toxicity of benzaldehyde.] Igiena, 16(1), 23.

Substance Name	Methyl 4-formylbenzoate
CAS No.	001571-08-0
Remarks for Substance	Data are for structurally related substance benzaldehyde
Method/guideline	Oral LD50 (calculated by using the Litchfield and Wilcoxon, dose range is 95 confidence interval)
Test Type	Acute oral toxicity
GLP	No
Year	1964
Species/strain	Rat/Osborne-Mendel
Sex	Male and Female

# of animals per sex per dose	5
Vehicle	Not reported
Route of Administration	Gavage
Remarks for Test Conditions	Five male and five female young adult Osborne-Mendel rats were fasted for 18 hours prior to treatment. Animals were observed for toxic signs and death. The observation period was up to 2 weeks.
Value LD50 or LC50 with confidence limits	LD50 = 1300 mg/kg bw (95% C.L. 1110-1540)
Number of deaths at each dose level	Not reported
Remarks for Results	Slope function: 1.4 (95% C.L. 1.2-1.6). Depression and coma were observed at higher doses. Time of deaths was between 4 and 18 hours.
Data Qualities Reliabilities	Reliability code 2. Reliable with restrictions.
Remarks for Data Reliability	Code 2. Acceptable, well-documented publication/study report, which meets basic scientific principles.
References	Jenner P.M., Hagen, E.C., Taylor, J.M., Cook, E.L., and Fitzhugh, O.G. (1964) Food flavourings and compounds of related structure. I. Acute oral toxicity. Fd Cosmet Toxicol., 2, 327-343.

Substance Name	Methyl 4-formylbenzoate
CAS No.	001571-08-0
Remarks for Substance	Data are for structurally related substance benzaldehyde
Method/guideline	Oral LD50 (calculated by using the Litchfield and Wilcoxon, dose range is 95 confidence interval)
Test Type	Acute oral toxicity
GLP	No
Year	1964
Species/strain	Guinea pig
Sex	Male and Female
# of animals per sex per dose	Not reported
Vehicle	Not reported
Route of Administration	Gavage
Remarks for Test Conditions	Groups of guinea pigs consisting of both males and females were fasted for 18 hours prior to treatment. Animals were observed for toxic signs and death. The observation period was up to 2 weeks.

	up to 2 weeks.
Value LD50 or LC50 with confidence limits	LD50 = 1000 mg/kg bw (95% C.L. 800-1250)
Number of deaths at each dose level	Not reported
Remarks for Results	Slope function: 1.4 (95% C.L. 1.2-1.8). Diuresis, tremors, intestinal irritation and haemorrhage were observed. Time of deaths was between 1 hour and 4 days.
Data Qualities Reliabilities	Reliability code 2. Reliable with restrictions.
Remarks for Data Reliability	Code 2. Acceptable, well-documented publication/study report, which meets basic scientific principles.
References	Jenner P.M., Hagen, E.C., Taylor, J.M., Cook, E.L., and Fitzhugh, O.G. (1964) Food flavourings and compounds of related structure. I. Acute oral toxicity. Fd Cosmet Toxicol., 2, 327-343.

Substance Name	Methyl 4-formylbenzoate
CAS No.	001571-08-0
Remarks for Substance	Data are for structurally related substance methyl benzoate
Method/guideline	Oral LD50 (calculated by using the Thompson method and tables of Weil)
Test Type	Acute oral toxicity
GLP	No
Year	1954
Species/strain	Rat/Carworth-Wistar
Sex	Male
# of animals per sex per dose	5
Vehicle	Not specified
Route of Administration	Gavage
Remarks for Test Conditions	Groups of 5 unfasted male rats were given a single dose of test substance in a logarithmic series. The animals were observed for up to 14 days.
Value LD50 or LC50 with confidence limits	LD50 = 3430 mg/kg bw (2.83-4.15 s.d.)
Number of deaths at each dose level	Not reported
Data Qualities Reliabilities	Reliability code 2. Reliable with restrictions.

Remarks for Data Reliability	Code 2. Acceptable, well-documented publication/study report, which meets basic scientific principles.
References	Smyth H.F., Carpenter, C.P., Weil, C.S., and Pozzani, U.C. (1954) Range-finding toxicity data: List V. Arch Ind Hyg Occupat Med 10(1), 61-68.

Substance Name	Methyl 4-formylbenzoate
CAS No.	001571-08-0
Remarks for Substance	Data are for structurally related substance methyl benzoate
Method/guideline	Oral LD50 (calculated by using the Berens method)
Test Type	Acute oral toxicity
GLP	No
Year	1970
Species/strain	Rat
Sex	Not reported
# of animals per sex per dose	24
Vehicle	2% starch solution
Route of Administration	Gavage
Remarks for Test Conditions	Groups of 24 rats were intragastrically administered 1000, 2000, 3000, 4000, or 5000 mg methyl benzoate/kg bw and were observed until death (within 14 days). The results were analyzed using the Berens method. Following death, the internal organs were macroscopically and pathologically examined.
Value LD50 or LC50 with confidence limits	LD50 = 3500 mg/kg bw
Number of deaths at each dose level	Not reported
Remarks for Results	Animals receiving the absolute lethal dose died within 2-3 hours. Initially following methyl benzoate administration, the animals became stimulated and slowly became uncoordinated, and breathing became rapid, spasms occurred and death due to cessation of respiration occurred. Animals receiving doses below the absolute lethal dose died within 14 days. There were no macroscopic lesions on the internal organs; however, the authors reported "severe expansion of the vessels in the liver" and "a plethora in the pulmonary tissue, expansion of the vessels, there were patches of vesicular emphysema with membrane rupture" in animals receiving the absolute lethal dose. The brain and adrenal gland showed no pathological changes.

Data Qualities Reliabilities	Reliability code 2. Reliable with restrictions.
Remarks for Data Reliability	Code 2. Basic data given: comparable to guidelines/standards.
References	Kravets-Bekker A.A., and Ivanova., O.P. (1970) Toxicological characteristics of methyl benzoate and potassium benzoate. Faktory Vneshn. Sredy Ikh Znach. Zdorov'ya Naseleniya, 1970(2), 125-129.

Substance Name	Methyl 4-formylbenzoate
CAS No.	001571-08-0
Remarks for Substance	Data are for structurally related substance methyl benzoate
Method/guideline	Oral LD50 (calculated by using the Berens method)
Test Type	Acute oral toxicity
GLP	No
Year	1970
Species/strain	Guinea pig
Sex	Not reported
# of animals per sex per dose	6
Vehicle	2% starch solution
Route of Administration	Gavage
Remarks for Test Conditions	Groups of 6 guinea pigs were intragastrically administered 2000, 3000, 4000, 5000, or 6000 mg methyl benzoate/kg bw and were observed until death (within 14 days). The results were analyzed using the Berens method. Following death, the internal organs were macroscopically and pathologically examined.
Value LD50 or LC50 with confidence limits	LD50 = 4100 mg/kg bw
Number of deaths at each dose level	Not reported
Remarks for Results	Animals receiving the absolute lethal dose died within 2-3 hours. Initially following methyl benzoate administration, the animals became stimulated and slowly became uncoordinated, and breathing became rapid, spasms occurred and death due to cessation of respiration occurred. Animals receiving doses below the absolute lethal dose died within 14 days. There were no macroscopic lesions on the internal organs; however, the authors reported "severe expansion of the vessels in the liver" and "a plethora in the pulmonary tissue, expansion of the vessels, there were patches of vesicular emphysema with membrane rupture" in animals receiving the absolute lethal dose. The brain and adrenal gland showed no pathological changes.

	changes.
Data Qualities Reliabilities	Reliability code 2. Reliable with restrictions.
Remarks for Data Reliability	Code 2. Basic data given: comparable to guidelines/standards.
References	Kravets-Bekker A.A., and Ivanova., O.P. (1970) Toxicological characteristics of methyl benzoate and potassium benzoate. Faktory Vneshn. Sredy Ikh Znach. Zdorov'ya Naseleniya, 1970(2), 125-129.

Substance Name	Methyl 4-formylbenzoate
CAS No.	001571-08-0
Remarks for Substance	Chemical assay: 60-65% Methyl 4-formylbenzoate; 18% methyl p-methylbenzoate
Method/guideline	Oral LD50
Test Type	Acute oral toxicity
GLP	No
Year	1970
Species/strain	Rat
Sex	Not reported
# of animals per sex per dose	10
Vehicle	10% in 0.5% aqueous guar gum
Route of Administration	Gavage
Remarks for Test Conditions	Groups of rats of unspecified strain were given dose levels of 200 to 3200 mg/kg orally by gavage. Time to death was 2 to 24 hours after dosing. Animals were observed for 2 weeks after dosing.
Value LD50 or LC50 with confidence limits	LD50 = 1600-3200 mg/kg
Number of deaths at each dose level	Not reported
Remarks for Results	Time to death 2 to 24 hours. Surviving animals showed slight weight gain 2 weeks after dosing. White crystals were observed in the urine.
Conclusion remarks	The acute oral LD50 of methyl 4-formylbenzoate in rats is in the range from 1600 to 3200 mg/kg bw.
Data Qualities Reliabilities	Reliability code 2. Reliable with restrictions.
Remarks for Data Reliability	Code 2. Basic data given: comparable to guidelines/standards.
References	Clark R.B. (1970) Toxicity Report to Eastman Kodak Co. Laboratory of Industrial Medicine. Report No 15928706. Private Communication to Chemintox Inc. Unpublished Report.

Communication to Chemintox Inc. Unpublished Report.

Substance Name	Methyl 4-formylbenzoate
CAS No.	001571-08-0
Remarks for Substance	Chemical assay: 60-65% Methyl 4-formylbenzoate; 18% methyl p-methylbenzoate
Method/guideline	Oral LD50
Test Type	Acute oral toxicity
GLP	No
Year	1970
Species/strain	Mouse
Sex	Not reported
# of animals per sex per dose	10
Vehicle	10% in 0.5% aqueous guar gum
Route of Administration	Gavage
Remarks for Test Conditions	Groups of mice of unspecified strain were given dose levels of 200 to 3200 mg/kg orally by gavage. Animals were observed for 2 weeks after dosing.
Value LD50 or LC50 with confidence limits	LD50 = 1600-3200 mg/kg
Number of deaths at each dose level	Not reported
Remarks for Results	Time to death 2 hours. Surviving animals showed slight weight gain 2 weeks after dosing. Animals showed slight to moderate weakness after dosing.
Conclusion remarks	The acute oral LD50 of methyl 4-formylbenzoate in mice is in the range from 1600 to 3200 mg/kg bw.
Data Qualities Reliabilities	Reliability code 2. Reliable with restrictions.
Remarks for Data Reliability	Code 2. Basic data given: comparable to guidelines/standards.
References	Clark R.B. (1970) Toxicity Report to Eastman Kodak Co. Laboratory of Industrial Medicine. Report No 15928706. Private Communication to Chemintox Inc. Unpublished Report.

Substance Name	Methyl 4-formylbenzoate
CAS No.	001571-08-0
Remarks for Substance	Data are for structurally related substance methyl benzoate

Method/guideline	Oral LD50 (calculated)
Test Type	Acute oral toxicity
GLP	No
Year	1945
Species/strain	Rat
Sex	Not reported
# of animals per sex per dose	Not reported
Vehicle	Not reported
Route of Administration	Gavage
Remarks for Test Conditions	A total of 25 rats were used to determine the LD50. Not less than 3 groups of 5 rats were tested. Rats were fasted 24 to 48 hours prior to administration of test substance. Rats were observed for 2 weeks or until death.
Value LD50 or LC50 with confidence limits	LD50 = 2170 mg/kg bw
Number of deaths at each dose level	Not reported
Remarks for Results	Overall intoxicated rats showed signs of central nervous system stimulation including: piloerection, muscular incoordination, progressive paralysis of the hind limbs and violent spastic convulsions, dyspnea and death (often preceded by respiratory paralysis).
Data Qualities Reliabilities	Reliability code 2. Reliable with restrictions.
Remarks for Data Reliability	Code 2. Basic data given: comparable to guidelines/standards.
References	Graham B.E. and Kuizenga, M.H. (1945) Toxicity studies of benzyl benzoate and related benzyl compounds. J Pharm Exp Ther., 84, 358-62.

Substance Name	Methyl 4-formylbenzoate
CAS No.	001571-08-0
Remarks for Substance	Data are for structurally related substance methyl benzoate
Method/guideline	Oral LD50 (calculated)
Test Type	Acute oral toxicity
GLP	No
Year	1945
Species/strain	Rabbit

Sex	Not reported
# of animals per sex per dose	Not reported
Vehicle	Not reported
Route of Administration	Gavage
Remarks for Test Conditions	A total of 12 rabbits were used to determine the LD50. Not less than 3 groups of 3 rabbits were tested. Rabbits were fasted 24 to 48 hours prior to administration of test substance. Rabbits were observed for 2 weeks or until death.
Value LD50 or LC50 with confidence limits	LD50 = 2170 mg/kg bw
Number of deaths at each dose level	Not reported
Remarks for Results	Overall intoxicated rabbits showed signs of central nervous system stimulation similar to that reported in rats [including: piloerection, muscular incoordination, progressive paralysis of the hind limbs and violent spastic convulsions, dyspnea and death (often preceded by respiratory paralysis)] followed by a 12- to 24-hour period of prostration prior to death.
Data Qualities Reliabilities	Reliability code 2. Reliable with restrictions.
Remarks for Data Reliability	Code 2. Acceptable, well-documented publication/study report, which meets basic scientific principles.
References	Graham B.E. and Kuizenga, M.H. (1945) Toxicity studies of benzyl benzoate and related benzyl compounds. J Pharm Exp Ther., 84, 358-62.

Substance Name	Methyl 4-formylbenzoate
CAS No.	001571-08-0
Remarks for Substance	Data are for structurally related substance methyl benzoate
Method/guideline	Oral LD50 (calculated by using the Berens method)
Test Type	Acute oral toxicity
GLP	No
Year	1970
Species/strain	Mouse/white
Sex	Not reported
# of animals per sex per dose	20
Vehicle	2% starch solution
Route of Administration	Gavage

Remarks for Test Conditions	Groups of 20 white mice were intragastrically administered 500, 1000, 2000, 3000, 3500, or 4000 mg methyl benzoate/kg bw and were observed until death (within 14 days). The results were analyzed using the Berens method. Following death, the internal organs were macroscopically and pathologically examined.
Value LD50 or LC50 with confidence limits	LD50 = 3000 mg/kg bw
Number of deaths at each dose level	Not reported
Remarks for Results	Animals receiving the absolute lethal dose died within 2-3 hours. Initially following methyl benzoate administration, the animals became stimulated and slowly became uncoordinated, and breathing became rapid, spasms occurred and death due to cessation of respiration occurred. Animals receiving doses below the absolute lethal dose died within 14 days. There were no macroscopic lesions on the internal organs; however, the authors reported "severe expansion of the vessels in the liver" and "a plethora in the pulmonary tissue, expansion of the vessels, there were patches of vesicular emphysema with membrane rupture" in animals receiving the absolute lethal dose. The brain and adrenal gland showed no pathological changes.
Data Qualities Reliabilities	Reliability code 2. Reliable with restrictions.
Remarks for Data Reliability	Code 2. Basic data given: comparable to guidelines/standards.
References	Kravets-Bekker A.A., and Ivanova., O.P. (1970) Toxicological characteristics of methyl benzoate and potassium benzoate. Faktory Vneshn. Sredy Ikh Znach. Zdorov'ya Naseleniya, 1970(2), 125-129.

4.2 Genetic Toxicity

4.2.1 *In vitro* Genotoxicity

Substance Name	Methyl 4-formylbenzoate
CAS No.	001571-08-0
Remarks for Substance	Data are for structurally related substance dimethyl terephthalate
Method/guideline	Ames reverse mutation

Year	1982, 1985
Species/Strain	*Salmonella typhimurium* TA98, TA100, TA1535, and TA1537
Metabolic Activation	With and without
Doses/Concentration	3.3 to 333 micrograms/plate
Results	With metabolic activation: 666 ug Without metabolic activation: 666 ug
Genotoxic Effects	None
Remarks for Results	Procedure: Pre-incubation Plates/test: Unknown Activation system: S-9 was from Aroclor 1254-induced male SD rats and Syrian hamsters. Media: Histidine selective Number of replicates: 2
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Basic data given: comparable to guidelines/standards.
References	Zeiger, E., Haworth, S., Speck, W., and Mortelmans, K. (1982) "Phthalate Ester Testing in the National Toxicology Program's Environmental Mutagenesis Test Development Program", Environmental Health Perspectives, 45:99-101. Zeiger, E., Haworth, S., Mortelmans, K., and Speck, W. (1985) "Mutagenicity Testing of Di(2-ethylhexyl)phthalate and Related Chemicals in Salmonella", Environmental Mutagenesis, 7:213-232.

Substance Name	Methyl 4-formylbenzoate
CAS No.	001571-08-0
Remarks for Substance	Data are for structurally related substance dimethyl terephthalate
Method/guideline	Chromosomal aberration and Sister chromatid exchange
Year	1990
Species/Strain	Chinese Hamster Ovary (CHO) cells
Remarks for Test Conditions	CHO cells were grown and treated under conditions similar to those described by Galloway et al., (1985). Aroclor-induced rat liver microsomal preparations were combined with cofactors and added as the metabolic activation system. Medium and solvent controls were used with each assay. Positive controls (Mitomycin C for use without the metabolic activation system and cyclophosphamide for use with the activation system) were also included. For sister chromatid exchange (SCE) experiments without metabolic activation, bromodeoxyuridine

	experiments without metabolic activation, bromodeoxyuridine (BRDU) was added 2-hours after the addition of the control or test substance and the culture continued for 24-hours. Fresh medium with BRDU and colcemid replaced the previous media and the cultures continued for 2.5-hours. For SCE experiments with metabolic activation, serum free medium with cofactors, S9 fraction, and chemical were used for 2-hours and replaced with medium containing BRDU and the culture continued for 24-hours. Colcemid was added to the media and the cultures continued for 2.5-hours. The cells were then examined for cytotoxicity, harvested and fixed. Fluorescence-microscopy was then used to assess the frequency of metaphase cells and SCE. For experiments examining chromosomal aberrations without metabolic activation, media with either the control or test substance was used for 8-hours and then removed. Media containing colcemid replaced the previous media and the cultures continued for 2.5-hours. For experiments with metabolic activation, serum free medium with cofactors, S9 fraction, and chemical were used for 2-hours, then the media removed and fresh media used for 8-hours. Colcemid was then added and incubations continued for 2-hours. Cells were harvested and slides prepared using a 5% Giemsa stain for five minutes. Two hundred cells per dose were scored for chromosomal aberrations.
Cytotoxic concentration	With metab. activ.: >10 ug/ml Without metab. activ.: >10 ug/ml
Genotoxic Effects	None
Remarks for Results	Procedure: CHO cells Plates/test: Unknown Activation system: Aroclor 1254-treated male SD rats Media: McCoy's 5A (modified media) buffered with 20 mM HEPES and supplemented with 10% FBS, 2 mM L-glutamine, 50 IU penicillin, and 50 µg/ml streptomycin.
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Acceptable, well-documented publication/study report, which meets basic scientific principles.
References	Loveday, K.S., Anderson, B.E., Resnick, M.A., and Zeiger, E. (1990) Chromosome Aberration and Sister Chromatid Exchange Tests in Chinese Hamster Ovary Cells In Vitro. V: Results with 46 Chemicals, Environmental and Molecular Mutagenesis, 16:272-303.

Substance Name	Methyl 4-formylbenzoate
CAS No.	001571-08-0
Remarks for Substance	Data are for structurally related substance dimethyl terephthalate

Test Type	DNA single-strand breaks
Year	1989,1991
Species/ Strain	Rat\Hepatocytes
Metabolic Activation	With
Doses/Concentration	0, 3.75, 7.50, or 15.00 µmole/ml equivalent to 0, 727.5, 1,455, or 2,910 µg/ml
Remarks for Test Conditions	DMT was dissolved in a mixture of DMSO and Tween 20 (29:1). Rat hepatocytes were isolated by conventional methods. Cytotoxicity (trypan blue exclusion) was measured following a 1-hour incubation period. The remaining cells were lysed and DNA was isolated on filters and eluted at alkaline pH. DNA was measured in the eluted fractions by fluorometric determinations using a Hoechst 33258 dye. A positive finding is designated when the percent DNA retained on the control filter minus the percent DNA retained on the filters from each treatment group is greater than 20% at dose levels with greater than 70% viability.
Results	Dimethyl terephthalate treatment did not produce any evidence of an increase in DNA single strand breaks.
Cytotoxic concentration	With metabolic activation: greater than 2,910 micrograms/ml Without metabolic activation: NA
Genotoxic Effects	None
Remarks for Results	Procedure: Primary rat hepatocytes were used Plates/test: Unknown Activation system: Primary rat hepatocytes Media: Unknown No. replicates: Unknown
Conclusion Remarks	Within the limitations of the test, dimethyl terephthalate is not genotoxic
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Basic data given: comparable to guidelines/standards.
References	Monarca, S., Pool-Zobel, B.L., Rizzi, R., Klein, P., Schmezer, P., Piatti, E., Pasquini, R., De Fusco, R., and Biscardi, D. (1991) In vitro Genotoxicity of Dimethyl Terephthalate. Mutation Research, 262:85-92. Monarca, S., Rizzi, R., Pasquini, R., Pool, B.L., De Fusco, R., Biscardi, D., Gervasoni, M., and Piatti, E. (1989) Studies on the Genotoxic Properties of Precursors of Polyethyleneterephthalate Plastics, Mutation Research, 216:314-315.

Substance Name	Methyl 4-formylbenzoate
CAS No.	001571-08-0
Remarks for Substance	Data are for structurally related substance dimethyl terephthalate
Method/guideline	Gene Mutation
Year	1991
Species/Strain	Mouse/L5178Y lymphoma cells (clone 3.7.2C.)
Doses/Concentration	0-100 ug/ml
Remarks for Test Conditions	Increases in the frequency of 5-trifluorothymidine(TFT)-resistant cells due to mutational events occurring at the thymidine kinase locus following DMT exposure (50 µg/ml) was determined with and without S9 fraction. Dimethylformamide (1%) was used as the solvent carrier. The treatment period was 4 hours at 37 °C in a roller drum (10-15 rpm). Cells were retrieved by centrifugation and washed twice with growth media. The two-day expression and growth period was conducted with cell densities of 3x105 cells/ml (20 ml of media on roller drum). After two-days, the cells were added to 90 ml of cloning media. Dishes containing the cells and cloning media were incubated for 11 to 12-days at 37 °C with 5% CO2/humidified air for colony development.
Cytotoxic concentration	With metabolic activation greater than 100 ug/ml Without metabolic activation greater than 100 ug/ml
Genotoxic Effects	None
Remarks for Results	Procedure: L5178Y mouse lymphoma cells (clone 3.7.2C.) Plates/test: Unknown Activation system: Aroclor 1254-induced male F344 rats Growth media: RPMI 1640 medium supplemented with heat-treated horse serum (10% v/v), 220 µg/ml sodium pyruvate, 2 mM L-glutamine, 0.05% Pluronic F68 and gentamycin (50 micrograms/ml) Treatment media: Fischer's growth medium with 5% heat-treated horse serum. Cloning media: Growth media plus 0.35-0.40% agar and 3 µg/ml TFT
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Acceptable, well-documented publication/study report, which meets basic scientific principles.
References	Myhr, B.C. and Caspary, W.J. (1991) Chemical Mutagenesis at the Thymidine Kinase Locus in L5178Y Mouse Lymphoma Cells: Results for 31 Coded Compounds in the National Toxicology Program, Environmental and Molecular Mutagenesis, 18:51-83.

Substance Name	Methyl 4-formylbenzoate
CAS No.	001571-08-0
Remarks for Substance	Data are for structurally related substance dimethyl terephthalate
Test Type	DNA single-strand breaks
Year	1989,1991
Species/Strain	SV40-transformed Chinese Hamster Embryo cell line (CO60 cells)
Metabolic Activation	Without
Doses/Concentration	0, 3.75, 7.50, or 15.00 µmole/ml equivalent to 0, 727.5, 1,455, or 2,910 micrograms/ml.
Remarks for Test Conditions	DMT was dissolved in a mixture of DMSO and Tween 20 (29:1). Cytotoxicity (trypan blue exclusion) was measured following a 1-hour incubation period. Cells were lysed and DNA was isolated on filters and eluted at alkaline pH. DNA was measured in the eluted fractions by fluorometric determinations using a Hoechst 33258 dye. A positive finding is designated when the percent DNA retained on the control filter minus the percent DNA retained on the filters from each treatment group is greater than 20% at dose levels with greater than 70% viability.
Results	Dimethyl terephthalate treatment did not produce any evidence of an increase in DNA singe strand breaks.
Cytotoxic concentration	Without metabolic activation: greater than 2,910 micrograms/ml
Genotoxic Effects	None
Remarks for Results	Procedure: SV40-transformed Chinese Hamster Embryo cell line (CO60 cells). Plates/test: Unknown Activation system: None Media: Unknown No. replicates: Unknown Other: Results of this test were not fully reported.
Conclusion Remarks	Dimethyl terephthalate was not genotoxic within the limitations of this test.
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Basic data given: comparable to guidelines/standards.
References	Monarca, S., Pool-Zobel, B.L., Rizzi, R., Klein, P., Schmezer, P., Piatti, E., Pasquini, R., De Fusco, R., and Biscardi, D. (1991) In vitro Genotoxicity of Dimethyl Terephthalate, Mutation Research, 262:85-92.

	Monarca, S., Rizzi, R., Pasquini, R., Pool, B.L., De Fusco, R., Biscardi, D., Gervasoni, M., and Piatti, E. (1989) "Studies on the Genotoxic Properties of Precursors of Polyethyleneterephthalate Plastics", Mutation Research, 216:314-315.

Substance Name	Methyl 4-formylbenzoate
CAS No.	001571-08-0
Remarks for Substance	Data are for structurally related substance dimethyl terephthalate
Test Type	Unscheduled DNA synthesis
Species/Strain	Human/Hela
Metabolic Activation	With and Without S-9 Activation
Doses/Concentration	5, 50, 500, 5,000 micrograms/ml
Remarks for Test Conditions	Induction of unscheduled DNA synthesis was measured in HeLa cells exposed to varying concentrations of DMT dissolved in a mixture of DMSO and Tween 20 (29:1). DMT exposures were conducted in PBS with or without S9 liver fractions. Following treatment and rinsing to remove residual material, the cells were incubated with or without hydroxyurea (HU) in culture media. Tritiated methylthymidine was added after 15 minutes and the incubations continued for three-hours. Radioactivity was then counted to determine the incorporation of the radiolabeled thymidine. Inhibition of DNA replication and synthesis by HU in the control and treated cultures was determined by comparing the ratio of counts from 1) control w/o HU ¸ control plus HU, and 2) treated w/o HU ¸ treated plus HU. Inhibition of DNA replication and synthesis by DMT exposure was determined by the ratio of treated w/o HU ¸ control w/o HU. The effect of HU on the induction of DNA repair in the presence of DMT was determined by the ratio of (treated plus HU ¸ treated w/o HU) divided by (control plus HU ¸ control w/o HU).
Results	Dimethyl terephthalate treatment did not produce any evidence of an increase in unscheduled DNA synthesis.
Cytotoxic concentration	With metabolic activation: Unknown Without metabolic activation.: Unknown
Genotoxic Effects	Dimethyl terephthalate did not induce any evidence
Remarks for Results	Procedure: Hela cells Plates/test: Unknown Activation system: S-9 was from Aroclor induced SD rats Media: Phosphate-buffered saline No. replicates: Unknown

Conclusion Remarks	Within the limitations of the test, dimethyl terephthalate is not genotoxic.
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Basic data given: comparable to guidelines/standards.
References	Monarca, S., Pool-Zobel, B.L., Rizzi, R., Klein, P., Schmezer, P., Piatti, E., Pasquini, R., De Fusco, R., and Biscardi, D. (1991) "In vitro Genotoxicity of Dimethyl Terephthalate", Mutation Research, 262:85-92. Monarca, S., Rizzi, R., Pasquini, R., Pool, B.L., De Fusco, R., Biscardi, D., Gervasoni, M., and Piatti, E. (1989) "Studies on the Genotoxic Properties of Precursors of Polyethyleneterephthalate Plastics", Mutation Research, 216:314-315

Substance Name	Methyl 4-formylbenzoate
CAS No.	001571-08-0
Remarks for Substance	Data are for structurally related substance methyl benzoate
Method/guideline	Paper disk method (Lyer and Szybalski, 1958)
Test Type	Reverse mutation test
System of Testing	Bacterial
GLP	No
Year	1958
Species/Strain	Sd-4-73 E. coli
Metabolic Activation	No
Doses/Concentration	Not reported
Statistical Methods	Not reported
Remarks for Test Conditions	*E. coli* was cultured overnight at 36 °C in an aerated nutrient broth containing 20 ug/ml streptomycin. Plates were prepared and methyl benzoate was added by applying to a paper disk, which was then placed on the agar. Relative mutagenicity, defined as “an approximate ratio of the number of colonies on the plate containing the mutagen to the number of colonies on the control plate”, was calculated. “Potent” mutagens had relative mutagenicities of greater than 3 and “weak and doubtful” mutagens had relative mutagenicities between 1.5 and 3.
Results	Methyl benzoate produced no increase in the frequency of reversion from streptomycin dependence to independence in Sd-4-73 *E. coli*.

Cytotoxic concentration	Not reported
Genotoxic Effects	None
Conclusion Remarks	Methyl benzoate was non mutagenic in this assay.
Data Qualities Reliabilities	Reliability code 2. Reliable with restrictions.
Remarks for Data Reliability	Study was conducted prior to establishment of GLP guidelines.
References	Szybalski W. (1958) Special microbiological systems. II. Observations on chemical mutagenesis in microorganisms. Annals New York Academy of Sciences. Pp 475-489.

Substance Name	Methyl 4-formylbenzoate
CAS No.	001571-08-0
Remarks for Substance	Data are for structurally related substance methyl benzoate
Method/guideline	Ames assay (Haworth et al., 1983)
Test Type	Reverse mutation test
System of Testing	Bacterial
GLP	Not reported
Year	1992
Species/Strain	*Salmonella typhimurium* TA100, TA1535, TA1537, TA97, TA98
Metabolic Activation	S9 fractions of Aroclor 1254-induced male Sprague-Dawley rats and male Syrian hamster livers
Doses/Concentration	0, 10, 33, 100, 333, 666, 1000, 1666, 3333, or 6666 ug/plate
Statistical Methods	
Remarks for Test Conditions	Sodium azide (TA1535 and TA100), 4-nitro-o-phenylenediamine (TA98 and 1538), mitomycin C (TA102), methyl methanesulfonate (TA104) and 9-aminoacridine (TA97 and TA1537) were used as positive controls for the specific Salmonella strains without S9. 2-Aminoanthracene was used with all strains incubated with S9 and either sterigmatocystin or 2-aminoanthracene was used for TA102.DMSO was used as the solvent control. Nine concentrations of the methyl benzoate (in triplicate) were incubated with or without S9 for 20 minutes after which plates were prepared and incubated at 37 °C for 48 hours. The number of revertants was machine counted. If a chemical was not active (with or without metabolic activation) in all Salmonella strains tested, it was considered non mutagenic.
Results	Methyl benzoate showed no mutagenic activity in any of the strains tested with or without S9.
Cytotoxic concentration	Not reported

Genotoxic Effects	None
Conclusion Remarks	Methyl benzoate was non mutagenic.
Data Qualities Reliabilities	Reliability code 1. Reliable without restriction.
Remarks for Data Reliability	Assay was conducted by standard methodology and published in a peer-reviewed journal. Tabulated results.
References	Zeiger E., Anderson, B., Haworth, S., Lawlor, T., and Mortelmans, K. (1992) Salmonella mutagenicity tests: V. Results from the testing of 311 chemicals. Environ Mol Mut., 19 (Suppl 21), 2-141.

Substance Name	Methyl 4-formylbenzoate
CAS No.	001571-08-0
Remarks for Substance	Data are for structurally related substance benzaldehyde
Method/guideline	Ames assay
Test Type	Reverse mutation test
System of Testing	Bacterial
GLP	Not reported
Year	1992
Species/Strain	*Salmonella typhimurium* TA100, TA102, TA104
Metabolic Activation	Rat liver microsome fraction S9 from Aroclor induced F344 rats and B6C3F1 mice
Doses/Concentration	Not reported
Statistical Methods	The data were evaluated using Wahrendorf ranking and Dunnett's t-test.
Remarks for Test Conditions	Cells were tested with and without S9.
Results	Benzaldehyde was non mutagenic with or without S9 in all *Salmonella* strains tested.
Cytotoxic concentration	Not reported
Genotoxic Effects	None
Conclusion Remarks	Benzaldehyde was non mutagenic in this assay.
Data Qualities Reliabilities	Reliability code 2. Reliable with restrictions.
Remarks for Data Reliability	Data from abstract only but method appears to be standard and results are consistent with chemical structure and other results.
References	Dillon D.M., McGregor, D.B., Combes, R.D. amd Zeiger, E. (1992) Detection of mutagenicity in Salmonella of some aldehydes and peroxides. Environ. Molec. Mutagen., 19(suppl 20), 15.

20), 15.

Substance Name	Methyl 4-formylbenzoate
CAS No.	001571-08-0
Remarks for Substance	Data are for structurally related substance benzaldehyde
Method/guideline	Ames assay
Test Type	Reverse mutation (spot test)
System of Testing	Bacterial
GLP	Not reported
Year	1980
Species/Strain	*Salmonella typhimurium* TA1535, TA1537, TA98, TA100
Metabolic Activation	With and without rat liver microsomes fraction S9 from Aroclor induced rats
Doses/Concentration	3 umol/plate
Remarks for Test Conditions	For each experiment viable count was determined, the number of spontaneous revertants was measured, the presence of the rfa-mutation was determined by crystal violet inhibition, the presence of the plasmid pKM 101 in strains TA98 and TA100 was determined by resistance to ampicillin, and the response to positive controls N-methyl-N-nitrosoquanidin (without metabolic activation) and 2-aminoanthracene (with activation) was determined. Spectroscopic-grade ethanol was used as the solvent. The test substance was tested at 3 umol/plate in TA98, TA100, TA1535, and TA1537 with or without S9. If there was no background lawn of bacteria, the tests were redone using lower concentrations. Uncertain results prompted the conduction of the tests at 4 concentration levels (0.03, 0.3, 3 and 30 umol/plate).
Results	Benzaldehyde produced a negative response in this assay.
Cytotoxic concentration	Not reported
Genotoxic Effects	None
Remarks for Results	Spot tests are less sensitive than quantitative experiments. Also, the results from strain TA100 are difficult to interpret because the high growth background (150-200 colonies per plate); however, spot tests provide a good "screening" method for large numbers of chemicals.
Conclusion Remarks	Benzaldehyde is non-mutagenic in the Ames assay using *Salmonella typhimurium* strains TA98, TA100, TA1535, and TA1537 with or without S9.
Data Qualities Reliabilities	Reliability code 1. Reliable without restriction.

Remarks for Data Reliability	Study is published in a peer-reviewed journal with adequate description and follows standard procedures.
References	Florin I., Rutberg, L., Curvall, M. and Enzell, C.R. (1980) Screening of tobacco smoke constitutents for mutagenicity using the Ames' test. Toxicology, 18, 219-232.

Substance Name	Methyl 4-formylbenzoate
CAS No.	001571-08-0
Remarks for Substance	Data are for structurally related substance benzaldehyde
Method/guideline	Ames assay
Test Type	Reverse mutation test
System of Testing	Bacterial
GLP	Not reported
Year	1989
Species/Strain	*Salmonella typhimurium* TA1535, TA1537, TA1538, TA98, TA100
Metabolic Activation	With and without rat liver microsome fraction S9 from Aroclor induced rats
Doses/Concentration	37500 ug/plate
Statistical Methods	Not reported
Remarks for Test Conditions	Following 2 days of incubation at 37 °C, revertant colonies were counted electronically.
Results	Benzaldehyde was inactive in the Ames assay using *Salmonella typhimurium* TA1535, TA1537, TA1538, TA98, TA100 with or without S9 activation.
Cytotoxic concentration	Not reported
Genotoxic Effects	None
Conclusion Remarks	Benzaldehyde was non-mutagenic in this assay.
Data Qualities Reliabilities	Reliability code 2. Reliable with restrictions.
Remarks for Data Reliability	Assay was conducted by standard methodology, but there was limited description of the study and the results were tabulated.
References	Heck J.D., Vollmuth, T.A., Cifone, M.A., Jagannath, D.R., Myhr, B. and Curren, R.D. (1989) An evaluation of food flavoring ingredients in a genetic toxicity screening battery. The Toxicologist, 9(1), 257.

Substance Name	Methyl 4-formylbenzoate

CAS No.	001571-08-0
Remarks for Substance	Data are for structurally related substance benzaldehyde
Method/guideline	Ames assay
Test Type	Reverse mutation test
System of Testing	Bacterial
GLP	Not reported
Year	1979
Species/Strain	*Salmonella typhimurium* TA98, TA100
Metabolic Activation	With rat liver microsome fraction S9
Doses/Concentration	Urinary metabolites assayed ranged from 0.05 to 100 ul/plate
Remarks for Test Conditions	0.5 ml benzaldehyde was administered by gavage to 2 Sprague-Dawley rats, which were kept in metabolism cages. Urine and feces were collected for 24 hours. Urine was separated from the feces and was prepared for mutagenicity screening. Bacterial cells were incubated with benzaldehyde in the presence of S9 for 48 hours at 37 C. Sodium azide and picrolonic acid were used as positive controls for TA100 and TA98, respectively. Enzyme activation by S9 was confirmed with plates containing aflatoxin B1.
Results	The urinary metabolites of benzaldehyde did not increase the number of revertants.
Cytotoxic concentration	Not reported
Genotoxic Effects	None
Remarks for Results	The urinary metabolites of benzaldehyde were non mutagenic in this assay.
Data Qualities Reliabilities	Reliability code 2. Reliable with restrictions.
Remarks for Data Reliability	Limited description of study and results.
References	Rockwell P. and Raw, I. (1979) A mutagenic screening of the various herbs, spices, and food additives. Nutrition and Cancer, 1(4), 10-16.

Substance Name	Methyl 4-formylbenzoate
CAS No.	001571-08-0
Remarks for Substance	Data are for structurally related substance benzaldehyde
Method/guideline	Ames assay
Test Type	Reverse mutation test

System of Testing	Bacterial
GLP	Not reported
Year	1998
Species/Strain	*Salmonella typhimurium* TA100, TA102, TA104
Metabolic Activation	With and without rat liver microsome fraction S9 (from Aroclor 1254-induced F344 rats and male B6C3F1 mice)
Doses/Concentration	33-3333 ug/plate
Statistical Methods	Dunnett's t-test, Wahrendorf ranking and linear regression
Results	Benzaldehyde produced no increase in reverse mutations.
Cytotoxic concentration	Not reported
Genotoxic Effects	None
Appropriate statistical evaluations?	Yes
Conclusion Remarks	Benzaldehyde was non mutagenic with or without metabolic activation.
Data Qualities Reliabilities	Reliability code 1. Reliable without restriction.
Remarks for Data Reliability	Assay was conducted using standard methodology and was published in a peer-reviewed journal.
References	Dillon D., Combes, R. and Zeiger, E. (1998) The effectiveness of Salmonella strains TA100, TA102 and TA104 for detecting mutagenicity of some aldehydes and peroxidies. Mutagen., 13(1), 19-26.

Substance Name	Methyl 4-formylbenzoate
CAS No.	001571-08-0
Remarks for Substance	Data are for structurally related substance benzaldehyde
Method/guideline	Ames assay
Test Type	Reverse mutation test
System of Testing	Bacterial
GLP	Not reported
Year	1982
Species/Strain	*Salmonella typhimurium* TA98, TA100
Metabolic Activation	Rat liver microsome fraction S9 from Aroclor induced rats
Doses/Concentration	0.05-500 ug/plate

Remarks for Test Conditions	DMSO was used as the solvent and control. The results were considered positive if a reproducible, dose-related increase in the number of revertants and a greater than 2-fold increase in spontaneous mutation rate was observed.
Results	Benzaldehyde did not increase the incidence of mutation as compared to the vehicle controls, either with or without S9 mix.
Cytotoxic concentration	Not reported
Genotoxic Effects	None
Conclusion Remarks	Benzaldehyde was non-mutagenic.
Data Qualities Reliabilities	Reliability code 2. Reliable with restrictions.
Remarks for Data Reliability	Assay was conducted by standard methodology and published in a peer-reviewed journal. Tabulated results.
References	Kasamaki A., Takahashi, H., Tsumura, N., Niwa, J., Fujita, T. and Urasawa, S. (1982) Genotoxiciy of flavoring agents. Mutat. Res., 105, 387-392.

Substance Name	Methyl 4-formylbenzoate
CAS No.	001571-08-0
Remarks for Substance	Data are for structurally related substance benzaldehyde
Method/guideline	Ames assay
Test Type	Reverse mutation test
System of Testing	Bacterial
GLP	Not reported
Year	1983
Species/Strain	*Salmonella typhimurium*TA98 and TA1535
Metabolic Activation	Not reported
Doses/Concentration	0, 0.1, 0.5, 1.0, 2.5, or 5.0 umol/plate
Statistical Methods	Mean of 3 values with extremes never removed from the means by greater than 5-10%.
Remarks for Test Conditions	The test substance was tested at 5 concentrations with 3 plates per concentration. The positive control for TA1535 was 2 ug sodium azide and for TA98 was 3 ug 2-nitrofluorene.
Results	There was no detectable mutagenic activity.
Cytotoxic concentration	Not reported
Genotoxic Effects	None
Conclusion Remarks	Benzaldehyde was non-mutagenic in this assay.

Data Qualities Reliabilities	Reliability code 1. Reliable without restriction.
Remarks for Data Reliability	Assay was conducted by standard methodology and published in a peer-reviewed journal.
References	Wiessler M. Romruen, K. and Pool, B.L. (1983) Biological activity of benzylating N-nitroso compounds. Models of activated N-nitrosomethylbenzylamine. Carcinogenesis, 4(7), 867-871.

Substance Name	Methyl 4-formylbenzoate
CAS No.	001571-08-0
Remarks for Substance	Data are for structurally related substance benzaldehyde
Method/guideline	Ames assay (Haworth et al., 1983)
Test Type	Reverse mutation test
System of Testing	Bacterial
GLP	Yes
Year	1990
Species/Strain	*Salmonella typhimurium* TA102, TA104, TA100, TA98, TA1535, and TA1537
Metabolic Activation	S9 mix from livers of Aroclor 1254-incude male SD rat or Syrian hamster
Doses/Concentration	TA102 (trial 1 and 2): 0, 33, 100, 333, 1,000 or 3,333 ug/plate; TA100 (trial 1): 0, 33, 100, 333, 1,000, or 3,333 ug/plate; TA100 (trial 2): 0, 10, 33, 100, 333, or 1,000 ug/plate; TA1535, TA1537 and TA98: 0, 10, 33, 100, 333, or 1,000 ug/plate
Remarks for Test Conditions	Tester strains and test substance or solvent were incubated with or without S9. Cytotoxicity limited highest concentration tested, but test concentration did not exceed 10 mg/plate. Positive controls used were 2-aminoanthracene, 4-nitro-o-phenylenediamine, sodium azide, and 9-aminoacridine. Tests with TA102, TA104 and TA100 were conducted at Inveresk Research International and with TA1535, TA1537 and TA98 at EG&G Mason Research Institute.
Results	All tester strains produced negative results. Cytotoxicity was observed at 1,000 and 3,333 ug/plate for TA100, at 3,333 ug/plate for TA102 and TA104, and at 1,000 ug/plate for TA98, TA1535 and TA1537.
Cytotoxic concentration	1,000 to 3,333 ug/plate
Genotoxic Effects	None
Conclusion Remarks	Benzaldehyde was non-mutagenic in this assay.
Data Qualities Reliabilities	Reliability code 1. Reliable without restriction.

Remarks for Data Reliability	NTP study
References	National Toxicology Program (1990) Toxicology and carcinogenesis studies of benzaldehyde (CAS No. 100-52-7) in F344/N rats and B6C3F1 mice. Technical Report Series 378.

Substance Name	Methyl 4-formylbenzoate
CAS No.	001571-08-0
Remarks for Substance	Data are for structurally related substance benzaldehyde
Method/guideline	Ames assay (modified)
Test Type	Reverse mutation test
System of Testing	Bacterial
GLP	No
Year	1978
Species/Strain	*Salmonella typhimurium* TA100, TA98
Metabolic Activation	Liver microsomal enzymes from KC-500 treated rats and "certain co-factors"
Doses/Concentration	Not reported
Statistical Methods	Not reported
Remarks for Test Conditions	The slight modification of the Ames assay was a preincubation of the samples for 15 min at 37 °C prior to plating. Benzaldehyde was tested with and without metabolic activation.
Results	No mutagenicity was reported.
Cytotoxic concentration	Not reported
Genotoxic Effects	None
Conclusion Remarks	Benzaldehyde was non-mutagenic in this assay.
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	The data were published in a brief abstract with limited detail and the study was conducted prior to GLP and OECD guidelines.
References	Sasaki Y. and Endo, R. (1978) Mutagenicity of aldehydes in Salmonella. Mutat Res., 54(2), 251.

Substance Name	Methyl 4-formylbenzoate
CAS No.	001571-08-0
Remarks for Substance	Data are for structurally related substance benzaldehyde

Method/guideline	Ames assay
Test Type	Reverse mutation test
System of Testing	Bacterial
GLP	No
Year	1980
Species/Strain	*Salmonella typhimurium* TA100
Metabolic Activation	None
Doses/Concentration	Not reported
Remarks for Test Conditions	The test was not conducted in duplicate and was part of a larger study examining the mutagenicity of aqueous chlorination of organic compounds.
Results	No mutagenicity was reported.
Cytotoxic concentration	Not reported
Genotoxic Effects	None
Conclusion Remarks	Benzaldehyde was non-mutagenic in this assay.
Data Qualities Reliabilities	Reliability code 3. Not reliable.
Remarks for Data Reliability	Assay was not conducted in accordance with current standards (lack of duplicates) and was not well described.
References	Rapson W.H., Nazar, M.A. and Butsky, V.V. (1980) Mutagenicity produced by aqueous chlorination of organic compounds. J Bull of Environ Contamination and Toxicology, 24(4), 590-596.

Substance Name	Methyl 4-formylbenzoate
CAS No.	001571-08-0
Remarks for Substance	Data are for structurally related substance benzaldehyde
Method/guideline	*Bacillus subtilis* recessive assay
Test Type	Reverse mutation test
System of Testing	Bacterial
GLP	No
Year	1978
Species/Strain	*Bacillus subtilis* M45 (Rec-) and H17 (Rec+)
Metabolic Activation	None

Doses/Concentration	21 ug/disk
Remarks for Test Conditions	The results were considered negative if the zone of inhibition was less than 2 mm, weakly positive if greater than or equal to 2 mm, and positive if greater than or equal to 5mm.
Results	Benzaldehyde produced negative results.
Genotoxic Effects	None
Conclusion Remarks	Benzaldehyde was non-mutagenic in this assay.
Data Qualities Reliabilities	Reliability code 2. Reliable with restrictions.
Remarks for Data Reliability	Code 2. Acceptable, well-documented publication/study report, which meets basic scientific principles.
References	Oda Y., Hamano, Y., Inoue, K., Yamamoto, H., Niihara, T. and Kunita, N. (1978) Mutagenicity of food flavours in bacteria. Obaka-Furitsu Koshu Eisei Kenyu, 9, 177.

Substance Name	Methyl 4-formylbenzoate
CAS No.	001571-08-0
Remarks for Substance	Data are for structurally related substance benzaldehyde
Method/guideline	*Bacillus subtilis* recessive assay
Test Type	Reverse mutation test
System of Testing	Bacterial
GLP	Not reported
Year	1989
Species/Strain	*Bacillus subtilis* M45 (arg-, trp-, recE-) and H17 (arg-, trp-, recE+)
Metabolic Activation	S9 mixture (not described)
Doses/Concentration	Not reported
Remarks for Test Conditions	Benzaldehyde was tested with and without metabolic activation. The data were evaluated several ways: (1) calculation of the 50% survival concentration from the benzaldehyde concentration giving 50% survival turbidity of Rec+ over benzaldehyde concentration giving 50% survival turbidity of Rec-; (2) probit analysis of the area enclosed (S-probit) between the plotted survival lines of Rec+ and Rec-; (3) mathematical calculation of "repaired survival" from a plot of mean lethal hits of Rec- against survival as the difference between Rec- and Rec+ curves; and (4) quantitative evaluation of DNA damaging potential expressed as Rec-gram=S-probit/benzaldehyde concentration giving 50% survival turbitity of Rec-.

Results	Without metabolic activation, benzaldehyde did not show any DNA damaging potential; however, when metabolically activated, benzaldehyde was considered to show DNA damaging potential. The authors conclusion was based only on the evaluation of the S-probit which was at the low end of the range of values considered to have DNA damaging potential. The repaired survival value calculated for benzaldehyde was well below the range considered to have DNA damaging potential.
Remarks for Results	The reviewer does not agree with the authors' conclusion of benzaldehyde's DNA damaging potential for several reasons: (1) the S-probit value (0.258) on which the conclusion was based just barely fell into the value range (0.200-0.592) listed in the criteria as having DNA damaging potential. Chemicals with strong DNA damaging potential had S-probit values of more than 0.593. (2) The value for "repaired survival" indicated no DNA damaging potential. (3) Chemicals tested by the authors as positive controls produced calculated values several fold higher than any calculated for benzaldehyde.
Conclusion Remarks	Benzaldehyde was reported to show DNA damaging potential based on one parameter examined. The weight of evidence indicates that benzaldehyde does not have DNA damaging potential.
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Although the study was well documented, the methodology used was not standard and the results were open to interpretation.
References	Matsui S., Yamamoto, R., and Yamada, H. (1989) The *Bacillus subtilis*/microsome Rec-assay for the detection of DNA damaging substances which may occur in chlorinated and ozonated waters. Wat Sci Tech., 21, 875-887.

Substance Name	Methyl 4-formylbenzoate
CAS No.	001571-08-0
Remarks for Substance	Data are for structurally related substance benzaldehyde
Method/guideline	Mouse lymphoma assay
Test Type	Forward mutation test
System of Testing	Non bacterial
GLP	Not reported
Year	1991
Species/Strain	L5178Y mouse lymphoma cell line
Metabolic Activation	Rat liver microsome fraction S9
Doses/Concentration	Trial #1: 0, 50, 100, 200, 400 or 800 ug/ml; Trial #2: 0, 80, 160, 320, 480, or 640 ug/ml

	320, 480, or 640 ug/ml
Statistical Methods	The data were evaluated using the dose-trend test (Barlow et al., 1972) and a variance of analysis of pair-wise comparisons.
Remarks for Test Conditions	DMSO was used as the solvent and control (4 cultures). Methanesulphonate at 15 ug/ml was used as the positive control (2 cultures). Four cultures for each concentration were prepared. Colonies were counted using an automated counter. If relative growth and/or cloning efficiency did not meet the predetermined quality control criteria, then the culture was rejected.
Results	Benzaldehyde significantly increased mutant fractions in both experiments without S9 but at concentrations close to cytotoxic levels. The lowest-observed-effective dose (LOED) was 400 ug/ml and concentrations of 640 ug/ml were lethal.
Cytotoxic concentration	640 ug/ml
Genotoxic Effects	Increase in mutational frequency at 640 ug/ml
Appropriate statistical evaluations?	Yes
Conclusion Remarks	Benzaldehyde increased mutant fractions but only at concentrations nearing lethal levels.
Data Qualities Reliabilities	Reliability code 1. Reliable without restriction.
Remarks for Data Reliability	NTP study guideline study
References	McGregor D.B., Brown, A.G., Howgate, S., McBride, D., Riach, C. and Caspary, W.J. (1991) Responses of the L5178Y mouse lymphoma cell forward mutation assay. V: 27 coded chemicals. Environ. Molec. Mutagen., 17, 196-219.

Substance Name	Methyl 4-formylbenzoate
CAS No.	001571-08-0
Remarks for Substance	Data are for structurally related substance benzaldehyde
Method/guideline	Mouse lymphoma assay (Clive *et al*., 1979)
Test Type	Forward mutation test
System of Testing	Non bacterial
GLP	Not reported
Year	1989
Species/Strain	L5178Y mouse lymphoma cell line
Metabolic Activation	With and without rat liver microsome fraction S9 and cofactors
Doses/Concentration	12.5-800 nl /ml (with and without S9), 25-600 nl/ml (without S9), 400-600 nl/ml (with S9)

Statistical Methods	Not reported
Remarks for Test Conditions	Cells were exposed to benzaldehyde for 4 hours, washed, incubated for 48 hours and then cloned. After 10-14 days, colonies were automatically counted. The ratio of mutant to viable colonies cloned without selective medium was considered to be the mutant frequency.
Results	No increase in mutagenesis (as compared to the negative controls) except at 400-600 nl/ml (with S9) where a 2.8-5.2 fold increase was observed.
Cytotoxic concentration	Not reported
Genotoxic Effects	Increased mutations with S9
Conclusion Remarks	Although benzaldehyde produced an increase in mutagenic activity at concentrations ranging from 400-600 nl/ml (with S9), no change in mutagenic activity was reported at the other concentration ranges (12.5-800 and 25-600 nl/ml) that also cover the range reportedly showing an effect. Without further detail regarding the study design, it is difficult to interpret the significance of the positive finding.
Data Qualities Reliabilities	Reliability code 2. Reliable with restrictions.
Remarks for Data Reliability	Assay was conducted by standard methodology, but there was limited description of the study and the results were tabulated.
References	Heck J.D., Vollmuth, T.A., Cifone, M.A., Jagannath, D.R., Myhr, B. and Curren, R.D. (1989) An evaluation of food flavoring ingredients in a genetic toxicity screening battery. The Toxicologist, 9(1), 257.

Substance Name	Methyl 4-formylbenzoate
CAS No.	001571-08-0
Remarks for Substance	Data are for structurally related substance benzaldehyde
Method/guideline	Sister chromatid exchange (Galloway *et al*., 1985)
Test Type	Clastogenic assay
System of Testing	Non bacterial
GLP	Ambiguous
Year	1987
Species/Strain	Chinese hamster ovary cells
Metabolic Activation	With and without rat liver microsome fraction S9 and cofactors
Doses/Concentration	5-160 ug/ml (without S9); 160-1600 ug/ml (with S9)
Statistical Methods	Linear regression analysis was used to test trend. A 20% absolute increase over the control, at each dose, was considered to be significant.

Remarks for Test Conditions	Chemical treatment periods were approximately 25 hours without S9 (after 2 hours of test chemical exposure, 5-bromodeoxyuridine was added) and 2 hours with S9 (after which 5-bromodexoyuridine was added). After treatment with hypotonic KCl, cells were fixed, stained and examined with fluorescent microscopy. 50 cells per dose were scored from the three highest concentrations when sufficient M2 cells were available, from the control groups.
Results	Benzaldehyde induced sister chromatid exchanges with and without metabolic activation.
Cytotoxic concentration	Not reported
Genotoxic Effects	Induction of sister chromatid exchanges
Remarks for Results	The induction of sister chromatid exchanges was positive without S9 and weakly positive with S9.
Conclusion Remarks	Benzaldehyde was an inducer of sister chromatid exchanges, but the effect was weak in the presence of metabolic activation.
Data Qualities Reliabilities	Reliability code 1. Reliable without restriction.
Remarks for Data Reliability	Assay was conducted by standard methodology and published in a peer-reviewed journal.
References	Galloway S.M., Armstrong, M.J., Reuben, C., Colman, S., Brown, B., Cannon, C., Bloom, A.D., Nakamura, F., Ahmed, M., Duk, S., Rimpo, J., Margolin, B.H., Resnick, M.A., Anderson, B. and Zeiger, E. (1987) Chromosomal aberrations and sister chromatid exchanges in chinese hamster ovary cells: Evaluations of 108 chemicals. Env. Molec. Mutagen., 10(10), 1-175.

Substance Name	Methyl 4-formylbenzoate
CAS No.	001571-08-0
Remarks for Substance	Data are for structurally related substance benzaldehyde
Method/guideline	Sister chromatid exchange (Jansson *et al*., 1986)
Test Type	Clastogenic assay
System of Testing	Non bacterial
GLP	Not reported
Year	1988
Species/Strain	Human lymphocytes
Metabolic Activation	Phytohemagglutinin-stimulated
Doses/Concentration	0-2.0 mM
Statistical Methods	The data were analyzed using linear regression by least squares and significance was tested at p less than 0.05, 0.01, and 0.001.

	and 0.001.
Remarks for Test Conditions	DMSO and ethanol were used as solvents and negative controls. The positive control used was styrene-7,8-oxide. After an exposure of 88 hours, the lymphocytes were treated with colchicine (50 ng/ml for 2 hours) and hypotonic KCl (0.075 M for 5-10 minutes). For each concentration tested (not specified), 25 metaphases from one culture were analysed.
Results	Statistically significant increase in sister chromatid exchanges (p less than 0.01) as compared to the vehicle control. The regression coefficient was 4.0 SCE/cell/mM.
Cytotoxic concentration	Not reported
Genotoxic Effects	Induction of sister chromatid exchanges
Appropriate statistical evaluations?	Significant at p less than 0.01, correlation coefficient of 0.93
Conclusion Remarks	Benzaldehyde induced sister chromatid exchanges in this assay.
Data Qualities Reliabilities	Reliability code 1. Reliable without restriction.
Remarks for Data Reliability	Assay was conducted by standard methodology and published in a peer-reviewed journal.
References	Jansson T., Curvall. M., Hedin, A. and Enzell, C. (1988) In vitro studies of the biological effects of cigarette smoke condensate. III. Induction of SCE by some phenolic and related constituents derived from cigarette smoke. Mutat Res., 206, 17-24.

Substance Name	Methyl 4-formylbenzoate
CAS No.	001571-08-0
Remarks for Substance	Data are for structurally related substance benzaldehyde
Method/guideline	Sister chromatid exchange
Test Type	Clastogenic assay
System of Testing	Non bacterial
Year	1989
Species/Strain	Chinese hamster K-1 ovary cells (ATCC)
Metabolic Activation	Mitomycin C (induction of SCEs)
Doses/Concentration	0, 3.3, 10, 33.3, 100, 333, or 1000 uM
Statistical Methods	Student's t-test
Remarks for Test Conditions	Chinese hamster ovary cells were exposed to mitomycin C for 21 hours and then cells were exposed to benzaldehyde for 1 cell cycle followed by addition of 5-bromodeoxyuridine 2 cell cycles prior to fixation. Fifty metaphases per culture were analyzed for sister chromatid exchanges with and without treatment with mitomycin C for SCE induction.

	treatment with mitomycin C for SCE induction.
Results	Benzaldehyde did not induce sister chromatid exchanges at concentrations up to 333 uM. The highest concentration was reported to be cytotoxic.
Cytotoxic concentration	1000 uM
Genotoxic Effects	None
Conclusion Remarks	Benzaldehyde produce any evidence of an increase in sister chromatid exchanges in this assay.
Data Qualities Reliabilities	Reliability code 2. Reliable with restrictions.
Remarks for Data Reliability	Published in peer review journal but limited description of protocol and tabulated results.
References	Sasaki Y.F., Imanishi, H., Ohta, T. and Shirasu, Y. (1989) Modifying effects of components of plant essence on the induction of sister-chromatid exchanges in cultured Chinese hamster ovary cells. Mutat. Res., 226, 103-110.

Substance Name	Methyl 4-formylbenzoate
CAS No.	001571-08-0
Remarks for Substance	Data are for structurally related substance benzaldehyde
Method/guideline	Chromosomal aberrations
Test Type	Clastogenic assay
System of Testing	Non-bacterial
GLP	Not reported
Year	1982
Species/Strain	Chinese hamster ovary cells
Metabolic Activation	Rat liver microsome fraction S9
Doses/Concentration	50 nM
Statistical Methods	Chi square test
Remarks for Test Conditions	DMSO was used as the solvent and control. Cells were exposed to the flavoring agent for 24 hours and then incubated another 24 hours without the flavor after which the cells were treated with colchicine for 2-3 hours. Cells were stained using Giemsa staining method. The scoring of about 200 metaphase spreads, containing 20-26 chromosomes was used to calculate the percentage of chromosomal aberrations.
Results	Benzaldehyde produced a significant difference in chromosomal aberrations compared to the vehicle control (p less than 0.001).

Cytotoxic concentration	Not reported
Genotoxic Effects	Induction of chromosomal aberrations
Appropriate statistical evaluations?	p less than 0.001
Conclusion Remarks	Benzaldehyde induced an increase in chromosomal aberrations in Chinese hamster ovary cells.
Data Qualities Reliabilities	Reliability code 2. Reliable with restrictions.
Remarks for Data Reliability	Assay was conducted by standard methodology and published in a peer-reviewed journal. Tabulated results.
References	Kasamaki A., Takahashi, H., Tsumura, N., Niwa, J., Fujita, T. and Urasawa, S. (1982) Genotoxicity of flavoring agents. Mutat. Res., 105, 387-392.

Substance Name	Methyl 4-formylbenzoate
CAS No.	001571-08-0
Remarks for Substance	Data are for structurally related substance benzaldehyde
Method/guideline	Chromosomal aberrations (Galloway *et al.,* 1985)
Test Type	Clastogenic assay
System of Testing	Chinese hamster ovary cells
GLP	Not reported
Year	1987
Species/Strain	Chinese hamster ovary cells
Metabolic Activation	With and without rat liver microsome fraction S9 and cofactors
Doses/Concentration	50-500 ug/ml (without S9); 160-1600 ug/ml (with S9)
Statistical Methods	Linear regression analysis, binomial sampling assumption, and Dunnett's method for multiple dose comparison were used to evaluate the data.
Remarks for Test Conditions	Positive controls consisted of treatment with mitomycin C, triethylenemelamine, or cyclophosphamide and negative controls were solvents used to dissolve the test chemical. Tests were carried out with (2-hr test substance exposure) or without S9 (exposure throughout incubation) activation (male Sprague-Dawley rat hepatocytes induced with Aroclor 1254). Cells were harvested 8-12 hours after the beginning of the treatment, yielding cells in mitosis. 100 cells were scored from each of the three highest dose groups having sufficient metaphases for analysis and from positive and solvent controls. All types of aberrations were recorded and they were grouped as either "simple", "complex", or "other" and "total".
Results	No aberration induction was observed.

Cytotoxic concentration	Not reported
Genotoxic Effects	None
Remarks for Results	Benzaldehyde was negative for chromosomal aberration induction.
Conclusion Remarks	Benzaldehyde did not induce chromosomal aberrations in this assay.
Data Qualities Reliabilities	Reliability code 1. Reliable without restriction.
Remarks for Data Reliability	Assay was conducted by standard methodology and published in a peer reviewed journal.
References	Galloway S.M., Armstrong, M.J., Reuben, C., Colman, S., Brown, B., Cannon, C., Bloom, A.D., Nakamura, F., Ahmed, M., Duk, S., Rimpo, J., Margolin, B.H., Resnick, M.A., Anderson, B. and Zeiger, E. (1987) Chromosomal aberrations and sister chromatid exchanges in chinese hamster ovary cells: Evaluations of 108 chemicals. Env. Molec. Mutagen., 10(10), 1-175.

Substance Name	Methyl 4-formylbenzoate
CAS No.	001571-08-0
Remarks for Substance	Data are for structurally related substance benzaldehyde
Method/guideline	Chromosomal aberrations
Test Type	Clastogenic assay
System of Testing	Non bacterial
GLP	No
Year	1985
Species/Strain	Chinese hamster cells
Metabolic Activation	S9 mixture (not described)
Doses/Concentration	0, 0.8, or 1.0 mg/ml without S9; 0, 0.8, 1.0, 1.2 mg/ml with S9
Remarks for Test Conditions	The solvent used was DMSO and the tests were conducted with and without S9. The percent of polyploid cells was reported, as was the frequency of aberrant cells.
Results	At 0, 0.8 and 1.0 mg/ml without S9, the percent polyploid was 0, 11 and 3 and the frequency of total aberrant cells was 2, 2, and 24%, respectively. At 0, 0.8, 1.0, and 1.2 mg/ml with S9, the percent polyploid was 0, 11, 5, and 0 and the frequency of total aberrant cells was 0, 2, 9, and 9%, respectively.
Genotoxic Effects	Induction of chromosomal aberrations without S9
Conclusion Remarks	Benzaldehyde was judged by the authors to be positive only without metabolic activation at the highest dose tested.

Data Qualities Reliabilities	Reliability code 2. Reliable with restrictions.
Remarks for Data Reliability	Although the data were presented in Japanese with English summary tables, the data were generated by a reputable group of researchers and it appeared that standard procedures were followed. The data were considered reliable.
References	Sofuni T., Hayashi, M., Matsuoka, A., Sawada, M., Hatanaka, M. and Ishidate, M. (Jr.). (1985) Mutagenicity tests on organic chemical contaminants in city water and related compounds. II. Chromosome aberration tests in cultured mammalian cells. Bull Nat Inst Hyg Sci, 103, 64.

Substance Name	Methyl 4-formylbenzoate
CAS No.	001571-08-0
Remarks for Substance	Data are for structurally related substance benzaldehyde
Method/guideline	Unscheduled DNA synthesis (Williams, 1977, 1980 and Butterworth *et al.,* 1987)
Test Type	DNA damage
System of Testing	Rat hepatocyte
GLP	Not reported
Year	1989
Species/Strain	Rat/Fischer and Sprague-Dawley
Doses/Concentration	251 ug/ml
Statistical Methods	Not reported
Remarks for Test Conditions	Rat hepatocytes were incubated in culture dishes for 18-20 hours with benzaldehyde. Concurrent cell counting or measurement of LDH release was used to determine relative cell survival. UDS was measured by electronically counting nuclear grains and calculating the net nuclear grain count (NNG). At each test concentration, 75-150 cells were analyzed. An increase in NNG of "at least 6 grains per nucleus above the concurrent solvent control value and/or an increase in the percent of nuclei having 6 or more net grains to at least 10% above the concurrent negative control" was considered a positive UDS response.
Results	Benzaldehyde treatment did not increase UDS compared to controls.
Cytotoxic concentration	Not reported
Genotoxic Effects	None
Conclusion Remarks	Benzaldehyde was not genotoxic in this assay.
Data Qualities Reliabilities	Reliability code 2. Reliable with restrictions.

Remarks for Data Reliability	Assay was conducted by standard methodology, but there was limited description of the study and the results were tabulated.
References	Heck J.D., Vollmuth, T.A., Cifone, M.A., Jagannath, D.R., Myhr, B. and Curren, R.D. (1989) An evaluation of food flavoring ingredients in a genetic toxicity screening battery. The Toxicologist, 9(1), 257.

4.2.2 *In vivo* Genotoxicity

Substance Name	Methyl 4-formylbenzoate
CAS No.	001571-08-0
Remarks for Test Substance	Data are for structurally related substance terephthalate acid
Method/guideline	OECD Guideline 474
Test Type	Mammalian Erythrocyte Micronucleus assay
Year	2001
Species/Strain	Mouse/ICR
Sex	Male and Female
Route of Administration	Intraperitoneal
Doses/Concentration	200, 400, and 800 mg/kg
Exposure Period	24 and 48 hours
Remarks for Test Conditions	Animals were about 6-8 weeks of age at study initiation. Animals (5/sex/group) were dosed ip with vehicle (negative control), 200, 400 or 800 mg/kg TPA, or 50 mg/kg cyclophosphamide (positive control) in corn oil in a volume of 20 ml/kg body weight and were sacrificed at 24 hours. Additional animals (5/sex/group) were treated with vehicle or 800 mg/kg TPA and sacrificed at 48 hours. An additional group of 5 males and 5 females were dosed with 800 mg/kg TPA as a replacement group in case of mortality. Bone marrow samples from animals sacrificed at 24 and 48 hours were scored under oil immersion (2000 polychromatic erythrocytes (PCE) per animal) for the presence of micronuclei. The number of micronucleated normocytes per 2000 PCE was also assessed. The proportion of PCE to total erythrocytes was also recorded on a per 1000 erythrocyte basis. Statistical significance for the incidence of micronucleated polychromatic erythrocytes was

	incidence of micronucleated polychromatic erythrocytes was determined using Kastenbaum-Bowman Tables.
Remarks for Results	Mortality was observed in 1/15 male mice that had been treated with 800 mg/kg TPA. One mouse from the replacement group was used in place of the animal that died. Clinical signs following treatment with either dose of TPA included lethargy and piloerection. Negative and positive control animals appeared normal during the course of the study. The total number of micronuclei observed per 20000 PCE in animals treated with vehicle, 200, 400 or 800 mg/kg for 24 hours was 4, 8, 5, and 4, respectively. The incidence of micronuclei in animals treated with 800 mg/kg also did not differ from the vehicle control at 48 hours (2/20000 vs. 8/20000, respectively). There was no difference between males and females. TPA was negative in the test. The test was valid, as the incidence of micronuclei in the vehicle control was not greater than 5/1000 PCE and the number of micronucleated cells in the positive controls (382/20000) was significantly different (p less than 0.05) from the vehicle control. Reductions (up to 9%) in the ratio of polychromatic erythrocytes to total erythrocytes were observed in some of the treated groups relative to the vehicle control, suggesting that the test article did not inhibit erythropoiesis. Greater reductions in this ratio were observed in animals treated with cyclophosphamide (25-29%).
Conclusion Remarks	Criteria for a valid test: The mean incidence of micronucleated polychromatic erythrocytes must not exceed 5/1000 polychromatic erythrocytes (0.5%) in the negative control vehicle. The incidence rate in the positive control group must be significantly increased relative to the negative control (p less than 0.05, Kastenbaum-Bowman Tables.
Data Qualities Reliabilities	Reliability code 1. Reliable without restriction.
Remarks for Data Reliability	Code 1. Comparable to guideline study.
References	Bioreliance (2001) Mammalian erythrocyte micronucleus test. Study No. AA41MJ.123.BTL for BP Amoco.

Substance Name	Methyl 4-formylbenzoate
CAS No.	001571-08-0
Remarks for Test Substance	Data are for structurally related substance dimethyl terephthalate
Test Type	Chromosomal aberration (micronucleus assay)
Year	1993
Species/Strain	Mouse/B6C3F1
Sex	Male and Female

Route of Administration	Intraperitoneal
Doses/Concentration	438 to 1,750 mg/kg
Exposure period	3 days
Remarks for Test Conditions	Mice (5-7) were exposed by ip injection to DMT (in a corn oil vehicle) over 3 consecutive days. The dose level used was the highest practical given the solubility problems with the test material. Animals were euthanized with CO2 24-hours after their last exposure. Bone marrow smears (2 per mouse) were prepared and fixed with absolute methanol and stained with acridine orange. Each slide was evaluated for the number of micronuclei in polychromatic erythrocytes among 2,000 polychromatic erythrocytes and percentage of polychromatic erythrocytes among 200 erythrocytes.
Effect on mitotic index or PCE/NCE ratio by dose level and sex	Control= 65% and 1,750mg/kg = 72%
Genotoxic effects	None
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Basic data given: comparable to guidelines/standards.
References	Shelby, M.D., Erexson, G.L., Hook, G.J. and Tice R.R. (1993) Evaluation of a Three-Exposure Mouse Bone Marrow Micronucleus Protocol: Results with 49 Chemicals. Environmental and Molecular Mutagenesis, 21:160-179.

Substance Name	Methyl 4-formylbenzoate
CAS No.	001571-08-0
Remarks for Substance	Data are for structurally related substance dimethyl terephthalate
Test Type	Chromosomal aberration (micronucleus assay)
Year	1988
Species/Strain	Mouse/(C57Bl/6j x CBA)F1
Sex	Male and Female
Route of Administration	Intraperitoneal
Doses/Concentration	0.20 to 1.00 mmole/kg
Exposure Period	1 day
Remarks for Test Conditions	A single 0.2 ml solution of DMT (dissolved in a DMSO vehicle) was injected intraperitoneally. The highest dose level used was limited due to the toxicity of the vehicle. Fifteen mice per exposure group were used, although lethality occurred in some animals, thereby reducing the sample sizes. Negative control groups (distilled water, or 0.2 ml DMSO) and a positive control group (methylnitrosourea) were included. Mice were killed by

	group (methylnitrosourea) were included. Mice were killed by cervical dislocation at 24, 48 and 72-hours post-treatment. Slides were prepared according to the method of Schmid (1976), dried at room temperature, and stained with May-Gruenwald and Giemsa stains. Polychromatic erythrocytes (1,000/mouse) were scored for the presence of micronuclei. After identifying 200 erythrocytes, the ratio of polychromatic erythrocytes to normochromatic erythrocytes was determined.
Effect on mitotic index or PCE/NCE ratio by dose level and sex	Control= 41%, DMSO = 43% and 1 mmol/kg= 37%
Remarks for results	The results of this study are particularly difficult to interpret. The data is not presented on a per mouse basis, but instead all of the data from the animals are lumped together as a group. Therefore, there is no mean and standard deviation for each group value. The distilled water negative control group (n=24) had a reported micronuclei frequency of 1.5%, although the time after treatment when this was determined was not reported. The use of DMSO as a solvent caused mortality in 21 of 270 mice after receiving either DMSO or DMSO and test material. The remaining live animals within each group were randomly selected to evaluate the micronucleus endpoint. The frequency of micronuclei in the DMSO negative control group decreases from 2.5% at 24-hours to 1.17% at 48-hours and further to 0.83% at 72-hours. The percentage of polychromatic erythrocytes in the DMSO solvent control group was significantly increased over the distilled water control group at 24-hours. Clearly the toxicity of DMSO was affecting the number of polychromatic erythrocytes and micronuclei in the DMSO solvent control group. All dose levels of DMT tested increased the frequency of micronuclei, although these findings were primarily restricted to the 24-hour observation point, coincidentally the time of greatest increase in micronuclei frequency due to the DMSO vehicle. The increased frequency of micronuclei at 48-hours were limited to the 3 highest dose levels tested and at 72-hours, the two highest dose levels tested. The highest dose was also considered to have caused bone marrow suppression. The pattern of the time course for micronuclei formation in the treated groups mimicked that observed for the DMSO vehicle control, suggesting an interaction between the two chemicals (DMSO and DMT) may have occurred. Therefore, poor study design and reporting along with solvent toxicity makes interpretation of this study problematic. The dose levels tested were much lower than those used in other mouse micronuclei studies with a corn oil vehicle (3 injections over 3-days; above) and the increased frequency of micronuclei due to DMT treatment is in contrast to the other negative mutagenicity and clastogenicity findings for this material.
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Basic data given: comparable to guidelines/standards.
References	Goncharova, R.I., Zabrejko, S., Kozachenko, V.I. and Pashin, Y.V. (1988) Mutagenic Effects of Dimethyl Terephthalate on Mouse Somatic Cells In Vivo. Mutation Research, 204:703-709.

Mouse Somatic Cells In Vivo. Mutation Research, 204:703-709.

Substance Name	Methyl 4-formylbenzoate
CAS No.	001571-08-0
Remarks for Test Substance	Data are for structurally related substance benzaldehyde
Method/guideline	Sex-linked recessive lethal (SLRL) assay
Test Type	Lethal mutation test
GLP	Not reported
Year	1985
Species/Strain	Drosophila melanogaster
Sex	Male
Route of Administration	Feed
Doses/Concentration	1,150 ppm
Exposure Period	3 days
Remarks for Test Conditions	Glass fiber discs, saturated with the test compound carried a 5% sucrose solution were used to expose day-old males (Canton-S) for 3 days in glass shell vials. Males were mated immediately after treatment with 3 new females for each of 3 broods. If no wild-type males were identified among 20 or more Basc males or Basc1 +/- females, then it was considered a lethal mutation. If a few F2 or F3 wild-type males survived at less than 5% of Basc males or Basc1 +/- females then it was considered a lethal mutation.
Genotoxic effects	None
Appropriate statistical evaluations	Yes. Cluster analysis by Poisson distribution; normal test of lethal frequencies after clusters removed.
Conclusion Remarks	No induction of SLRL in Drosophila melanogaster.
Data Qualities Reliabilities	Reliability code 1. Reliable without restriction.
Remarks for Data Reliability	Code 1. Comparable to guideline study.
References	Woodruff R.C., Mason, J.M., Valencia, R. and Zimmering, S. (1985) Chemical mutagenesis testing in Drosophila. V. Results of 53 coded compounds for the national testing program. Environ Mutagen., 7, 677-702.

Substance Name	Methyl 4-formylbenzoate
CAS No.	001571-08-0

Remarks for Test Substance	Data are for structurally related substance benzaldehyde
Method/guideline	Sex-linked recessive lethal (SLRL) assay
Test Type	Lethal mutation test
GLP	Not reported
Year	1985
Species/Strain	Drosophila melanogaster
Sex	Male
Route of Administration	Injection
Doses/Concentration	2,500 ppm
Exposure Period	Single dose
Remarks for Test Conditions	Males (Canton-S) aged 2-3 days were intraperitoneally injected with a 0.7% NaCl solution containing benzaldehyde. At 24-48 hours post injection males were mated with 3 new females for each of 3 broods. If no wild-type males were identified among 20 or more Basc males or Basc1 +/- females, then it was considered a lethal mutation. If a few F2 or F3 wild-type males survived at <5% of Basc males or Basc1 +/- females then it was considered a lethal mutation.
Genotoxic effects	None
Appropriate statistical evaluations	Yes. Cluster analysis by Poisson distribution; normal test of lethal frequencies after clusters removed.
Conclusion Remarks	No induction of SLRL in Drosophila melanogaster.
Data Qualities Reliabilities	Reliability code 1. Reliable without restriction.
Remarks for Data Reliability	Code 1. Comparable to guideline study.
References	Woodruff R.C., Mason, J.M., Valencia, R. and Zimmering, S. (1985) Chemical mutagenesis testing in Drosophila. V. Results of 53 coded compounds for the national testing program. Environ Mutagen., 7, 677-702.

4.3 Repeated Dose Toxicity

Substance Name	Methyl 4-formylbenzoate
CAS No.	001571-08-0
Method/guideline	90-Day dietary study
GLP	No
Year	1972
Species/strain	Rat/Wistar
Sex	Male and Female
Route of Administration	Diet
Doses/concentration Levels	3% (30,000 ppm) in diet
Exposure Period	90 days
Frequency of Treatment	Daily
Control Group	Basal diet
Post exposure observation period	No
Remarks for Test Conditions	Animals were fed 5% terephthalic acid in the diet for 1 week, which was then reduced to 3% for the remainder of the study.
Toxic Response/effects by Dose Level	Formation of bladder stones and hyperplasia of the bladder urothelium
Remarks for Results	Pathological effects were limited to the kidney and bladder. Terephthalic acid induced bladder stones in 11/18 males and 3/19 females. Mild to moderate hyperplasia of the bladder urothelium was diagnosed in 13/18 males and 3/19 females. A strong correlation was found between the presence of uroliths and the development of bladder hyperplasia: 62% of the TPA males (8/13) and 100% of the TPA females (3/3) diagnosed as having transitional cell hyperplasia also had bladder stones. It is possible that microscopic calculi were passed or were lost during sectioning of bladder tissue for histopathology. This could explain the failure to detect uroliths in all of the hyperplastic bladders.
Data Qualities Reliabilities	Reliability code 2. Reliable with restrictions.
Remarks for Data Reliability	Comparable to guideline study with acceptable restrictions.
References	Amoco Corporation (1972) Subacute Feeding Studies (13 Week) In Rats with Dimethylterephthalate (DMT), Isophthalic Acid (IA) and Terephthalic Acid (TA). Conducted by Food and Drug Research Laboratories. FDRL Study #0411.

Substance Name	Methyl 4-formylbenzoate
CAS No.	001571-08-0
Method/guideline	28-Day inhalation study
GLP	No
Year	1973
Species/strain	Rat
Sex	Male and Female
Route of Administration	Inhalation
Doses/concentration Levels	0, 0.52, 1.2, 3.3 mg/m3
Exposure Period	28 days
Frequency of Treatment	6 hours per day for 4 weeks
Post exposure observation period	3 days
Toxic Response/effects by Dose Level	Minimal irritation and degeneration of tracheal epithelium at 3.3 mg/m3
Remarks for Results	No deaths occurred in the study. No differences were observed in clinical chemistry, hematology, body or organ weight changes. Histopathological findings consisted of minimal tracheal epithelial lining degeneration observed in 19/20 high-exposure rats, compared to 1/20 in control rats. There were no differences in any measured physiological parameters between control and high-exposure groups. In follow-up work, the incidence of minimal degeneration changes in the epithelial lining of the trachea was 5%, 30%, 65%, and 95% at exposures of 0, 0.52, 1.2, and 3.3 mg/m3, respectively.
Conclusion Remarks	Except for tracheal irritation from particulate terephthalic acid, no other effects were observed.
Data Qualities Reliabilities	Reliability code 3. Not reliable.
Remarks for Data Reliability	Methodology was unconventional and there was only use of 1 dose. No statistical analyses were conducted and results were not clearly described.
References	Amoco Corporation (1973) 4-Week Inhalation Toxicity Study of Terephthalic Acid (TA) In Rats. Conducted by IIT Research Institute. IITRI Study #1104.

Substance Name	Methyl 4-formylbenzoate
CAS No.	001571-08-0
Remarks for Test Substance	Data are for in vivo metabolite terephthalic acid

Method/guideline	Carcinogenicity
GLP	No
Year	1974
Species/strain	Rat/Wistar
Sex	Male and Female
Route of Administration	Diet
Doses/concentration Levels	1% (500 mg/kg/day) & 2% (1000 mg), 5% (2500 mg)
Exposure Period	2 years
Frequency of Treatment	Daily
Control Group	Basal diet
Post exposure observation period	No
NOAEL(NOEL)	There was no statistically significant increase in bladder tumors at 500 mg/kg bw/day
LOAEL(LOEL)	1000 mg/kg bw/day
Toxic Response/effects by Dose Level	Significant increase in bladder tumors at 5%
Remarks for Results	Reduced body weight gain occurred at in the 5% dose level (males and females) and in the 2% dose level (males). At 1%, reduced relative liver weight in females and reduced relative kidney size in males and females. At 2%, reduced liver, kidney, and heart weights (females only). At 5%, there was increased kidney weight in males, and increased adrenal weights in males and females; as well as increased mortality, mainly as a result of increased incidence of bladder stones (at 5%: males, 42/47; females, 39/42; at 1%: females, 1/48). There was increased incidence of bladder and ureter tumors (at 5%: males, 21/37; females, 21/34; at 2%: males, 1/48; females, 2/48; at 1%: males, 1/43.). There was increased incidence of bladder and ureter tumors.
Data Qualities Reliabilities	Reliability code 2. Reliable with restrictions.
Remarks for Data Reliability	Comparable to guideline study with acceptable restrictions.
References	Gross J. (1974) The effects of prolonged feeding of terephthalic acid (TPA) to rats. Project FG-IS-175. Submitted to US Dept. of Agriculture, Agriculture Research Service, Washington D.C.

Substance Name	Methyl 4-formylbenzoate
CAS No.	001571-08-0
Remarks for Test Substance	Data are for in vivo metabolite terephthalic acid

Method/guideline	15-Week dietary study
GLP	No
Year	1970
Species/strain	Rat/albino
Sex	Male and Female
Route of Administration	Diet
Doses/concentration Levels	0.05, 0.16, 0.50, 1.6, and 5.0% in the diet
Exposure Period	15 weeks
Frequency of Treatment	Daily in the diet
Control Group	Basal diet
Post exposure observation period	None
Remarks for Test Conditions	Animals (66-79 gram range) were divided into 7 groups of 60 each (30/sex) that corresponded to 2 control groups and 5 test groups (0.05, 0.16, 0.50, 1.6 and 5.0% test material in diet). Food and water were supplied ad libitum. Parameters assessed included: survival, clinical observations, growth, food consumption, hematology, serum clinical chemistries, urinalysis, gross pathology, and weights and histology of a full range of organs. Sacrifices were completed on 6 rats (3/sex) on Days 30, 60, and 90. All remaining animals were terminated on Day 105. Data were analyzed using analysis of variance and Duncan multiple range tests.
NOAEL(NOEL)	1.6% (approximately 1220 mg/kg in males and 1456 mg/kg in females)
LOAEL(LOEL)	5.0% (approximately 3837 mg/kg in males and 4523 mg/kg in females)
Toxic Response/effects by Dose Level	Survival: 4 animals (one male at 0.5% (Day 56) and three females in the highest dose (Days 54, 87, and 90) died of unknown etiology. Clinical signs: Hematuria was noted on a sporadic basis in the latter two thirds of the study in males treated with 5.0%. Growth: Body weights from both sexes treated with 5.0% were mildly depressed. Food Intake: No effects were noted. Hematology: No effects were noted. Clinical Chemistry: No effects were noted. Urinalysis: The only noteworthy finding was evidence of occult blood. Positive values were sporadically observed in males of all dose groups (except the lowest level) and in females at all treatment levels (number of animals affected was not listed). Occult blood was noted primarily at the 3 month examination time point except in the high dose animals of both sexes which

	showed evidence at 30, 60, and 90 days. It was usually noted as small. Gross Pathology: Findings of interest were limited to the urinary bladder. Calculi were noted in males treated with 5% (3/3 at 30 days, 2/3 at 60 days, 2/3 at 90 days, and 9/17 at 105 days). Organ Weights: No differences were noted that were deemed attributable to exposure to test material. Microscopic Pathology: Proliferative changes (hyperplasia) were noted in the urinary bladder and occasionally the kidney pelvis epithelium of all test groups and controls. These changes were significantly increased in both their incidence and severity in high dose (5%) males. This observation was deemed inconclusive in high dose females.
Appropriate statistical evaluations?	Duncan multiple range test
Remarks for Results	The hyperplastic change noted in the bladder is believed to be secondary to the chronic irritation induced by the presence of calculi. The bladder calculi and subsequent inflammation and hyperplasia seem to be threshold effects in that only animals in the high dose group (5%) displayed this pattern of pathology.
Conclusion Remarks	The NOAEL listed is for the critical effect (bladder calculi and subsequent hyperplasia). Doses of 0.05%, 0.16%, 0.5%, 1.6% and 5% corresponded to approximately 37.9, 122, 393, 1220 and 3837 mg/kg in males and 46, 147, 447, 1456 and 4523 mg/kg in females, respectively (based on average body weight and food intake).
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Comparable to guideline study with acceptable restrictions.
References	Amoco Corporation (1970) Fifteen Week Oral Toxicity of Terephthalic Acid – Albino Rats. Conducted by Toxicological Evaluations. LSL Study#1358.

Substance Name	Methyl 4-formylbenzoate
CAS No.	001571-08-0
Remarks for Test Substance	Data are for in vivo metabolite terephthalic acid
GLP	No
Year	1981
Species/strain	Rat
Sex	Male and Female
Route of Administration	Diet
Doses/concentration Levels	0.5, 1.5, 3.0, 4.0, or 5.0%

Exposure Period	14 days
Frequency of Treatment	Daily
Control Group	Basal diet
Post exposure observation period	No
Remarks for Test Conditions	Rats (13-18/sex/dose group) were fed DMT diets for a period of two-weeks. Individual body weights and total feed and water intake per cage were collected. At necropsy, urine was collected directly from the bladder for pH measurement, and concentrations of "stone-forming" materials were determined. The urinary system was examined grossly for presence of macroscopic calculi. Any calculi were collected, dried, weighed and analyzed. This study also evaluated terephthalic acid (TPA) at similar dietary levels
NOAEL(NOEL)	3% in the diet
LOAEL(LOEL)	5% in diet
Toxic Response/effects by Dose Level	Formation of urinary bladder calculi at 5% dietary levels
Remarks for Results	Exposure resulted in a 93.3% incidence of bladder calculi in male pups receiving 5% dietary terephthalic acid (TPA). Female pups also developed stones, but at a lower frequency. The dose-response curves for stone induction were extremely steep: no stones were induced at dietary concentrations below 1.5%. Histological examination of the urinary tract revealed extensive hyperplasia of the transitional epithelium only in the urinary bladders that contained calculi. Analysis of calculi indicated a heterogeneous chemical composition. The principal components (by weight) were: TPA, calcium, phosphate, and protein in the TPA-induced stones. Concentrations of calcium, TPA, and phosphate, as well as pH, were determined in the urine of weanling rats at study termination. TPA induced urinary acidosis and hypercalciuria in the range of doses used. Results indicate that critical saturating urinary concentrations of TPA and calcium are necessary for stones to develop following TPA exposure, and that calculus formation appears to be a prerequisite for the induction of TPA-induced bladder hyperplasia.
Data Qualities Reliabilities	Reliability code 2. Reliable with restrictions.
Remarks for Data Reliability	Comparable to guideline study with acceptable restrictions.
References	Chin T.Y., Tyl, R.W., Popp, J.A. and Heck, H. d'A. (1981) "Chemical Urolithiasis: 1. Characteristics of Bladder Stone Induction by Terephthalic Acid and Dimethyl Terephthalate in Weanling Fischer-344 Rats." Tox. and Appl. Pharm. 58:307-321.

Substance Name	Methyl 4-formylbenzoate

CAS No.	001571-08-0
Remarks for Test Substance	Data are for in vivo metabolite terephthalic acid
GLP	No
Year	1967
Species/strain	Rat/White
Sex	Male and Female
Route of Administration	Gavage
Doses/concentration Levels	10/rat on alternate days (approximately 20 mg/kg bw/d)
Exposure Period	12 weeks
Frequency of Treatment	Alternate days
Control Group	Not described
Post exposure observation period	None
Remarks for Test Conditions	Benzaldehyde was administered orally to adult white rats at doses of 10 mg diluted in 0.1 ml of oil on alternate days for a period of 12 weeks. 32 rats were divided into 4 groups, 2 of which were administered benzaldehyde in 2 different diet blends (18 or 8% casein). The other 2 groups were not described.
Actual dose received by dose level and sex	Approximately 20 mg/kg bw/d
Toxic Response/effects by Dose Level	There were no effects on growth, liver or adrenal gland weight.
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Study translated from foreign article with very limited description.
References	Sporn A., Dinu, I., and Stanclu, V. (1967) Cercetari cu privire la toxicitatea aldehidei benzoice. [Research regarding the toxicity of benzaldehyde.] Igiena, 16(1), 23.

Substance Name	Methyl 4-formylbenzoate
CAS No.	001571-08-0
Remarks for Test Substance	Data are for in vivo metabolite terephthalic acid
Method/guideline	Carcinogenicity study
GLP	No
Year	1983

Species/strain	Rat/Wistar
Sex	Male and Female
Route of Administration	Diet
Doses/concentration Levels	20, 142, 1000 mg/kg/day
Exposure Period	2 years
Frequency of Treatment	Daily
Control Group	Basal diet
NOAEL(NOEL)	142 mg/kg bw/day
LOAEL(LOEL)	1000 mg/kg bw/day
Toxic Response/effects by Dose Level	Induction of bladder stones in high dose females
Remarks for Results	Terephthalic acid induced bladder stones were seen in 13/126 females in the high dose group. At the scheduled 6 and 12-month sacrifices, no bladder calculi were detected. At the 18-month sacrifice sand like particle or bladder calculi were only seen in two of the high dose females. The high-dose corresponds to an approximate dietary concentration of 2.0 to 2.8% in adult F-344 rats.
Conclusion Remarks	A NOAEL was established as 142 mg/kg bw/day for female rats and 1000 mg/kg bw/day for male rats
Data Qualities Reliabilities	Reliability code 2. Reliable with restrictions.
Remarks for Data Reliability	Comparable to guideline study with acceptable restrictions.
References	Chemical Industry Institute of Technology (CIIT) (1983) Chronic Dietary Administration Of Terephthalic Acid. CIIT Docket 20124

Substance Name	Methyl 4-formylbenzoate
CAS No.	001571-08-0
Remarks for Test Substance	Data are for in vivo metabolite terephthalic acid
Method/guideline	3-month gavage study
GLP	Not reported
Year	1970
Species/strain	Mouse/White
Sex	Male and Female
Route of Administration	Gavage
Doses/concentration Levels	80 mg/kg bw/d

Exposure Period	3 months
Frequency of Treatment	Daily
Control Group	Not reported
Post exposure observation period	Not reported
Remarks for Test Conditions	Groups of 50 male and 50 female crossbred white mice (strain not specified) were administered 80 mg benzoic acid/kg bw/d by oral intubation for 3 months.
Toxic Response/effects by Dose Level	Weight gain of the treated animals was reduced compared to control animals.
Remarks for Results	The reduced body weight gain was reported not to be due to reduced feed intake, but it may have been due to stress factors such as food restriction, low temperature, swimming test, centrifugation, carbon tetrachloride detoxication test or kidney function testing.
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Very limited description of study and results.
References	Shtenberg A.J. and Ignat'ev A.D. (1970) Toxicological evaluation of some combinations of food preservatives. Food and Cosmetics Toxicology, 8, 369-380.

Substance Name	Methyl 4-formylbenzoate
CAS No.	001571-08-0
Remarks for Test Substance	Data are for dimethyl terephthalate
GLP	No
Year	1981
Species/strain	Rat
Sex	Male and Female
Route of Administration	Diet
Doses/concentration Levels	0, 0.5, 1.0, 1.5, 2, or 3% (females: 638, 1277, 1790, 2290, and 3020 mg/kg; males: 660, 1320, 1890, 2260, and 2590 mg/kg)
Exposure Period	14 days
Frequency of Treatment	Daily
Control Group	Basal diet
Post exposure observation period	No
Remarks for Test Conditions	Rats (13-18/sex/dose group) were fed DMT diets for a period of two-weeks. Individual body weights and total feed and water intake per cage were collected. At necropsy, urine was

	intake per cage were collected. At necropsy, urine was collected directly from the bladder for pH measurement, and concentrations of "stone-forming" materials were determined. The urinary system was examined grossly for presence of macroscopic calculi. Any calculi were collected, dried, weighed and analyzed. This study also evaluated terephthalic acid (TPA) at similar dietary levels.
NOAEL(NOEL)	0.5% (660 mg/kg) (males); 1.0% (1277 mg/kg) (females)
LOAEL(LOEL)	1.5% in diet
Toxic Response/effects by Dose Level	Formation of bladder calculi at 1.5, 2.0, and 3.0% dimethyl terephthalate
Remarks for Results	Average BW of the animals consuming the 1.5% and above was decreased on study Days 6-8 and 12-14 (postnatal Days 34-36 and 40-42) in females and 1.0% in males. Decreases in BW were accompanied by reduced feed consumption (possible palatability problems). There was no effect on water consumption at any dose. The incidence of bladder calculi in males from the 0, 0.5, 1.0, 1.5, 2.0, and 3.0% DMT dietary groups were 0, 0, 0, 35, 72, and 100%, respectively. The incidence of bladder calculi in females from the 0, 0.5, 1.0, 1.5, 2.0, and 3.0% DMT dietary groups were 0, 0, 0, 0, 36, and 47%, respectively. Grossly observable irregular thickening of the bladder wall was limited to animals having bladder calculi. The composition of the bladder calculi from the DMT treated animals was primarily calcium and terephthalic acid (TPA) with 5-7% protein. Phosphate levels were low, in contrast to bladder calculi from animals treated directly with terephthalic acid. Neither oxalate, nor uric acid, was found in the calculi. An acidic urinary pH was believed to have induced the hypercalciuria, a characteristic of urolithiasis in man. The higher urinary concentrations of TPA from DMT in the diet (when compared to similar dietary concentrations of TPA) explained the higher incidence of urinary calculi from the DMT diets than from comparable levels of TPA in the diet. Urinary phosphate levels were decreased in the animals consuming the DMT diet and explained why phosphate was present only at very low levels in the bladder calculi in those animals.
Data Qualities Reliabilities	Reliability code 2. Reliable with restrictions.
Remarks for Data Reliability	Comparable to guideline study with acceptable restrictions.
References	Chin, T.Y., Tyl, R.W., Popp, J.A. and Heck, H. d'A. (1981) "Chemical Urolithiasis: 1. Characteristics of Bladder Stone Induction by Terephthalic Acid and Dimethyl Terephthalate in Weanling Fischer-344 Rats." Tox. and Appl. Pharm. 58:307-321.

Substance Name	Methyl 4-formylbenzoate
CAS No.	001571-08-0
Remarks for Test Substance	Data are for structurally related substance methyl benzoate

Method/guideline	1.5-month toxicity study
GLP	No
Year	1970
Species/strain	Rat/white (strain not specified)
Sex	Not reported
Route of Administration	Not specified
Doses/concentration Levels	111 or 500 mg/kg bw/d
Exposure Period	45 days
Frequency of Treatment	Daily
Control Group	Yes, but not described
Remarks for Test Conditions	The study was translated from a Russian study and some of the methodology was difficult to interpret. Based on the previous acute portion of the study, it appears that methyl benzoate was administered by gavage; however in a discussion of some results, the authors indicate that a "preparation" was given by intraperitoneal injection. General condition and some hematology were evaluated once every 10-11 days and at the end of the study a necropsy was performed.
LOAEL(LOEL)	111 mg/kg bw/d
Toxic Response/effects by Dose Level	At 111 mg/kg bw/d, there was a statistically significant increase in blood erythrocytes ($p<0.05$) and reticulocytes significantly increased. At 500 mg/kg bw/d there was no change in "red blood", but a significant increase in "white blood" ($p<0.01$) and in the number of reticulocytes. There was a significant increase in prothrombin time ($p<0.01$) at both doses and a tendency for a decreased phagocytic index (authors reported this to occur in mice, but the reviewer assumes this is a typographical error and "rats" was intended) at 500 mg/kg bw/d. Whole blood cholinesterase activity was significantly decreased at the high dose. No histological findings were reported, although it was reported that the level of ascorbic acid in the adrenal glands was decreased in rats given 500 mg methyl benzoate/kg bw/d.
Remarks for Results	The results were difficult to interpret due to the poor translation of the article. The exact administration route and schedule were not clearly indicated and it is possible that additional groups were tested.
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	The study was translated from a foreign article and the data were collected prior to GLP and OECD guidelines and although the acute portion of this study received a code 2, the description of the subacute portion of the study is not well documented and difficult to interpret. Therefore the data are not considered reliable.

References	Kravets-Bekker A.A., and Ivanova., O.P. (1970) Toxicological characteristics of methyl benzoate and potassium benzoate. Faktory Vneshn. Sredy Ikh Znach. Zdorov'ya Naseleniya, 1970(2), 125-129.

Substance Name	Methyl 4-formylbenzoate
CAS No.	001571-08-0
Remarks for Test Substance	Data are for structurally related substance methyl benzoate
Method/guideline	6-month toxicity study
GLP	No
Year	1970
Species/strain	Rat/white (strain not specified) and grey rat
Sex	Not reported
Route of Administration	Not specified
Doses/concentration Levels	0.005 or 0.05 mg/kg bw/d
Exposure Period	6 months
Frequency of Treatment	Daily
Control Group	Yes, but not described
Remarks for Test Conditions	The study was translated from a Russian study and some of the methodology was difficult to interpret. Based on the previous acute portion of the study, it appears that methyl benzoate was administered by gavage; however in a discussion of some results, the authors indicate that a "preparation" was given by intraperitoneal injection. General condition and some hematology were evaluated once every 10-11 days and at the end of the study a necropsy was performed. In addition, the grey rats were studied for conditional reflexes using a food motive method and the white rats were studied for biochemical parameters.
NOAEL(NOEL)	0.005 mg/kg bw/d
LOAEL(LOEL)	0.05 mg/kg bw/d
Toxic Response/effects by Dose Level	The general condition of the animals in both dose groups did not differ from controls. At the high dose, there was decrease in the number of reticulocytes ($p<0.01$). There was no difference from controls in prothrombin time or phagocytic activity at either dose. In the grey rats, at the high dose, the latent period for response to "bell" or "light" stimulus was increased. Also, there was an increase in the number of sulfhydryl groups in cerebral tissue of high-dose grey rats. At necropsy, congestion and swelling of the hepatic central veins and capillaries was reported in high-dose rats. There were no histological findings

	in the low-dose animals.
Remarks for Results	The results were difficult to interpret due to the poor translation of the article. The exact administration route and schedule were not clearly indicated.
Conclusion Remarks	The authors reported that methyl benzoate administered at 0.005 mg/kg bw/d to rats did not produce adverse effects.
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	The study was translated from a foreign article and the data were collected prior to GLP and OECD guidelines and although the acute portion of this study received a code 2, the description of the chronic portion of the study is not well documented and difficult to interpret. Therefore the data are not considered reliable.
References	Kravets-Bekker A.A., and Ivanova., O.P. (1970) Toxicological characteristics of methyl benzoate and potassium benzoate. Faktory Vneshn. Sredy Ikh Znach. Zdorov'ya Naseleniya, 1970(2), 125-129.

Substance Name	Methyl 4-formylbenzoate
CAS No.	001571-08-0
Remarks for Test Substance	Data are for structurally related substance sodium benzoate
Method/guideline	Carcinogenicity assay
Year	1984
Species/strain	Mouse/albino Swiss
Sex	Male and Female
Route of Administration	Drinking water
Doses/concentration Levels	2% in the drinking water (approximately 4,000 mg/kg bw/d)
Exposure Period	Life span (up to approximately 112 weeks)
Frequency of Treatment	Daily
Control Group	Untreated drinking water
Post exposure observation period	None
Remarks for Test Conditions	Groups of 50 male and 50 female 5-week-old albino Swiss mice were administered sodium benzoate at a concentration of 2% in the drinking water (approximately 4,000 mg/kg bw/d) for their life span (up to approximately 112 weeks). Control groups consisted of 100 untreated mice per sex. Mice were examined clinically, weighed and gross pathological changes were recorded. Complete necropsies were conducted on all mice and organs were examined macroscopically and selected tissues (liver, spleen, kidney, bladder, thyroid, heart, pancreas, testes, ovaries, brain, nasal turbinates, and lung) were

	testes, ovaries, brain, nasal turbinates, and lung) were histopathologically examined.
Toxic Response/effects by Dose Level	Sodium benzoate administration had no effect on survival or on tumor incidence.
Conclusion Remarks	Sodium benzoate at a lifetime exposure of 2% in the drinking water of mice showed no evidence of carcinogenicity.
Data Qualities Reliabilities	Reliability code 2. Reliable with restrictions.
Remarks for Data Reliability	The protocol and results were reported in a short communication and statistical analyses were not reported.
References	Toth B. (1984) Lack of tumorigenicity of sodium benzoate in mice. Fundam Appl Toxicol., 4, 494-496.

Substance Name	Methyl 4-formylbenzoate
CAS No.	001571-08-0
Remarks for Test Substance	Data are for structurally related substance benzoic acid
Method/guideline	17-month oral toxicity study
GLP	Not reported
Year	1970
Species/strain	Mouse
Sex	Male and Female
Route of Administration	Oral
Doses/concentration Levels	40 mg/kg bw/d
Exposure Period	17 months
Frequency of Treatment	Daily
Control Group	Not reported
Post exposure observation period	Not reported
Remarks for Test Conditions	Groups of 25 male and 25 female mice were orally administered 40 mg benzoic acid/kg bw/d for 17 months.
Toxic Response/effects by Dose Level	Survival (%) at 2.5 months was greater for the benzoic acid group (68%) than that for the control group of males (60%) or female rats (62%).
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Very limited description of study and results.
References	Shtenberg A.J. and Ignat'ev A.D. (1970) Toxicological evaluation of some combinations of food preservatives. Food and Cosmetics Toxicology, 8, 369-380.

Substance Name	Methyl 4-formylbenzoate
CAS No.	001571-08-0
Remarks for Test Substance	Data are for structurally related substance benzoic acid
Method/guideline	3-month gavage study
GLP	No
Year	1970
Species/strain	Mouse/cross-bred white
Sex	Male and Female
Route of Administration	Gavage
Doses/concentration Levels	80 mg benzoic acid/kg bw/d or 80 mg benzoic acid/kg bw/d plus 160 mg sodium bisulphite/kg bw/d
Exposure Period	3 months
Frequency of Treatment	Daily
Control Group	Basal diet only
Remarks for Test Conditions	Groups of 50 male and 50 female cross-bred white mice were administered 80 mg benzoic acid/kg bw/d by gavage for 3 months. Similarly, groups of 50 male and 50 female cross-bred white mice were administered 80 mg benzoic acid/kg bw/d in conjunction with 160 mg sodium bisulphite/kg bw/d. Observations consisted of general condition, behaviour, and survival. Food consumption and body weight gain were recorded daily. Additionally, mice were tested to determine the possible effects of hunger, physical stress, and poisoning with carbon tetrachloride (single dose of 0.1 ml/mouse). A co-carcinogenicity test was conducted with Ehrlich ascites carcinoma. A control group was used but not described.
LOAEL(LOEL)	80 mg/kg bw/d
Toxic Response/effects by Dose Level	Survival was decreased at 2.5 months in animals given the benzoic acid/sodium bisulphite combination. Percent survival was 60, 68, and 30% for control mice, benzoic acid-fed mice, and benzoic acid/sodium bisulphite combination-fed mice, respectively. Treated animals did not gain weight to the same extent as controls (no statistical analysis) and did not appear to be associated with feed intake. Under 90% feed restriction conditions, treated mice showed greater mortality and weight loss than controls. Treated mice also appeared to be more sensitive to carbon tetrachloride poisoning. In the co-carcinogenicity tests, tumor growth appeared to be increased in treated animals compared to controls (data not shown by the study authors).
Conclusion Remarks	It appeared that benzoic acid administered at 80 mg/kg bw/d produced a reduction in body weight gain; however, no statistical analyses were conducted. In addition, benzoic acid

	statistical analyses were conducted. In addition, benzoic acid in combination with sodium bisulphite appeared to decrease survival.
Data Qualities Reliabilities	Reliability code 3. Not reliable.
Remarks for Data Reliability	Methodology was unconventional and there was only use of 1 dose. No statistical analyses were conducted and results were not clearly described.
References	Shtenberg A.J., and Ignat'ev, A.D. (1970) Toxicological evaluation of some combinations of food preservatives. Fd Cosmet Toxicol., 8, 369-380.

Substance Name	Methyl 4-formylbenzoate
CAS No.	001571-08-0
Remarks for Test Substance	Data are for structurally related substance benzoic acid
Method/guideline	18-month oral toxicity study
GLP	No
Year	1970
Species/strain	Rat/Wistar
Sex	Male and Female
Route of Administration	Oral
Doses/concentration Levels	40 mg benzoic acid/kg bw/d or 40 mg benzoic acid/kg bw/d plus 80 mg sodium bisulphite/kg bw/d
Exposure Period	18 months
Frequency of Treatment	Daily
Control Group	Basal diet only
Post exposure observation period	None
Remarks for Test Conditions	In an 18-month study, groups of 10 male and 10 female Wistar rats were fed 40 mg benzoic acid/kg bw/d in a paste prior to normal feeding. Similarly, groups of 50 male and 50 female Wistar rats were fed 40 mg benzoic acid/kg bw/d in conjunction with 80 mg sodium bisulphite/kg bw/d. Control animals received basal diet only. Parameters measured were food and water consumption, and body weight gain. Also, possible stress factors (low temperature tolerance) were recorded. Titre of serum complement, phagocytic activity of leucocytes, serum-ceruloplasmin level, blood alkalinity, blood ketones, blood morphology, erythrocyte sedimentation rate and C-reactive protein in serum were estimated.
NOAEL(NOEL)	40 mg/kg bw/d

Toxic Response/effects by Dose Level	The results were not clearly reported; however, it appeared that survival was decreased in rats fed the benzoic acid/sodium bisulphite combination and that the benzoic acid/sodium bisulphite combination-fed rats showed more of an effect in the stress tests, had increased erythrocyte sedimentation rates, and a decreased level of blood ketones compared to controls. No effects on blood alkalinity, C-reactive protein levels and blood morphology were reported in the treated rats. Apparently, small groups of benzoic acid-fed rats and benzoic acid/sodium bisulphite combination-fed rats were administered a lethal dose of sodium benzoate, to which the benzoic acid-fed rats appeared to have gained tolerance (25,100, and 100% mortality in benzoic acid-fed rats, benzoic acid/sodium bisulphite combination-fed rats, and controls, respectively).
Conclusion Remarks	A combination of benzoic acid and sodium bisulphite apparently decreased survival in rats; however, no statistical analysis was conducted and only 1 dose level was tested.
Data Qualities Reliabilities	Reliability code 3. Not reliable.
Remarks for Data Reliability	Methodology was unconventional and there was only use of 1 dose. No statistical analyses were conducted and results were not clearly described.
References	Shtenberg A.J., and Ignat'ev, A.D. (1970) Toxicological evaluation of some combinations of food preservatives. Fd Cosmet Toxicol., 8, 369-380.

Substance Name	Methyl 4-formylbenzoate
CAS No.	001571-08-0
Remarks for Test Substance	Data are for structurally related substance benzaldehyde
Method/guideline	14-day inhalation study
Year	1991
Species/strain	Rat/Sprague-Dawley
Sex	Male and Female
Route of Administration	Inhalation
Doses/concentration Levels	500, 750, or 1,000 ppm
Exposure Period	14 days
Frequency of Treatment	6 hours/day
Control Group	Filtered air
Post exposure observation period	Up to 72 hours
Remarks for Test Conditions	Groups of 14 male and 14 female Sprague-Dawley rats were exposed to 500, 750, or 1,000 ppm benzaldehyde, 6 hours/day for 14 consecutive days in 2.5 m3 chambers with an air flow rate of 500 L/min (Laham et al., 1991). Body weights were

	rate of 500 L/min (Laham et al., 1991). Body weights were recorded after day 2, 8 and 14. At necropsy, blood samples were collected for hematological and biochemical analyses, and gross pathological and histopathological examinations were conducted.
LOAEL(LOEL)	500 ppm
Toxic Response/effects by Dose Level	In the first week, 10 females and 1 male from the 1,000 ppm group and 1 female from the 750 ppm group died. Two more females were moribund in the second week. At all exposure groups, a mild irritation of the mucosa was reported with effects on the central nervous system including tremors, hypothermia, reduced breathing rates and decreased motor activity. At 1,000 ppm, hemoglobin and hematocrit counts were decreased in both sexes. Red blood cells also were decreased in high-dose females. A dose-related increase in monocytes was observed in females. Also in females, significant changes in total protein, albumin fraction, and serum cholinesterase were reported. Aspartate aminotransferase was significantly increased at all exposures in both males and females. In males, goblet cell metaplasia (largely confined to the respiratory epithelium lining the nasal septum) was reported; however the incidence and severity were similar in all treatment groups. There was no change in females.
Appropriate statistical evaluations?	Yes. Results analyzed using Duncan's multiple range test and a modified least significant difference procedure. Differences between groups determined with Student's t-test.
Remarks for Results	The authors suggested that the reported goblet cell metaplasia corresponded to a “mild form of adaptation during the recovery period following the inhalation exposure to benzaldehyde”.
Conclusion Remarks	A NOAEL could not be determined, but the authors concluded that typical human exposure levels are so small (5.3-22.5 ppb) that they should not be considered hazardous.
Data Qualities Reliabilities	Reliability code 1. Reliable without restrictions.
Remarks for Data Reliability	Although it was not reported whether this study was conducted under GLP, it was well reported and conducted by the Canadian Health Protection Branch. The data are considered reliable.
References	Laham S., Broxup, B., Robinet, M., Potvin, M., and Schrader, K. (1991) Subacute inhalation toxicity of benzaldehyde in the Sprague-Dawley rat. Am Ind Hyg Assoc J., 52(12), 503-510.

Substance Name	Methyl 4-formylbenzoate
CAS No.	001571-08-0
Remarks for Test Substance	Data are for structurally related substance benzaldehyde
Method/guideline	8-week gavage study
GLP	No

Year	1967
Species/strain	Rat/White
Sex	Male and Female
Route of Administration	Gavage
Doses/concentration Levels	10 mg/rat on alternate days (approximately 20 mg/jkg bw/d)
Exposure Period	8 weeks
Frequency of Treatment	Alternate days
Control Group	Not described
Post exposure observation period	None
Remarks for Test Conditions	Benzaldehyde was administered orally to adult white rats at doses of 10 mg diluted in 0.1 ml of oil on alternate days for a period of 8 weeks. Animals were killed and livers were examined for biochemical changes.
Actual dose received by dose level and sex	Approximately 20 mg/kg bw/d
Toxic Response/effects by Dose Level	No hepatic enzyme activity was reported.
Remarks for Results	Not described
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Study translated from foreign article with very limited description.
References	Sporn A., Dinu, I., and Stanclu, V. (1967) Cercetari cu privire la toxicitatea aldehidei benzoice. [Research regarding the toxicity of benzaldehyde.] Igiena, 16(1), 23.

Substance Name	Methyl 4-formylbenzoate
CAS No.	001571-08-0
Remarks for Test Substance	Data are for structurally related substance benzaldehyde
Method/guideline	Screening method used by U.S. Food and Drug Administration
GLP	No
Year	1967
Species/strain	Rat/Osborne-Mendel
Sex	Male and Female
Route of Administration	Diet

Doses/concentration Levels	10,000 ppm
Exposure Period	16 weeks
Frequency of Treatment	Daily
Control Group	Basal diet
Post exposure observation period	None
Remarks for Test Conditions	Groups of 5 male and 5 female Osborne-Mendel rats were provided test substance in the diet at concentrations of 0 or 10,000 ppm for 16 weeks. No vehicle was used. The diet was prepared and analyzed weekly. Measurements of body weight, food intake and general condition were recorded weekly. Hematological examinations (white cell counts, red cell counts, hemoglobins and hematocrits) were performed at the termination of the study. Macroscopic examination of all tissues was performed. Histopathological examination was performed on the liver, kidneys, spleen, heart, and testes of 6-8 animals (evenly divided by sex) from the high dose and controls.
Actual dose received by dose level and sex	Approximately 500 mg/kg bw/d
Toxic Response/effects by Dose Level	No effects were reported.
Conclusion Remarks	No effect reported at 10,000 ppm benzaldehyde in the diet of rats.
Data Qualities Reliabilities	Reliability code 2. Reliable with restrictions.
Remarks for Data Reliability	This study was performed by the Food and Drug Administration prior to the establishment of GLP and OECD. Data are considered reliable.
References	Hagan E.C., Hansen W.H., Fitzhugh O.G., Jenner P.M., Jones W.I., Taylor J.M., Long E.L., Nelson A.A., and Brouwer J.B. (1967) Food flavourings and compounds of related structure. II. Subacute and chronic Toxicity. Food Cosmet Toxicol 5:141-157.

Substance Name	Methyl 4-formylbenzoate
CAS No.	001571-08-0
Remarks for Test Substance	Data are for structurally related substance benzaldehyde
Method/guideline	Screening method used by U.S. Food and Drug Administration
GLP	No
Year	1967
Species/strain	Rat/Osborne-Mendel
Sex	Male and Female

Route of Administration	Diet
Doses/concentration Levels	1,000 ppm
Exposure Period	27-28 weeks
Frequency of Treatment	Daily
Control Group	Basal diet
Post exposure observation period	None
Remarks for Test Conditions	Groups of 5 male and 5 female Osborne-Mendel rats were provided test substance in the diet at concentrations of 0 or 1,000 ppm for 27-28 weeks. No vehicle was used. The diet was prepared and analyzed weekly. Measurements of body weight, food intake and general condition were recorded weekly. Hematological examinations (white cell counts, red cell counts, hemoglobins and hematocrits) were performed at the termination of the study. Macroscopic examination of all tissues was performed. Histopathological examination was performed on the liver, kidneys, spleen, heart, and testes of 6-8 animals (evenly divided by sex) from the high dose and controls.
Actual dose received by dose level and sex	Approximately 50 mg/kg bw/d
Toxic Response/effects by Dose Level	No effects were reported.
Conclusion Remarks	No effect reported at 1,000 ppm benzaldehyde in the diet of rats.
Data Qualities Reliabilities	Reliability code 2. Reliable with restrictions.
Remarks for Data Reliability	This study was performed by the Food and Drug Administration prior to the establishment of GLP and OECD. Data are considered reliable.
References	Hagan E.C., Hansen W.H., Fitzhugh O.G., Jenner P.M., Jones W.I., Taylor J.M., Long E.L., Nelson A.A., and Brouwer J.B. (1967) Food flavourings and compounds of related structure. II. Subacute and chronic Toxicity. Food Cosmet Toxicol., 5, 141-157.

Substance Name	Methyl 4-formylbenzoate
CAS No.	001571-08-0
Remarks for Test Substance	Data are for structurally related substance benzaldehyde
Method/guideline	16-day gavage study
GLP	Yes
Year	1990
Species/strain	Rat/F344/N

Sex	Male and Female
Route of Administration	Gavage
Doses/concentration Levels	0, 100, 200, 400, 800, or 1,600 mg/kg bw/d
Exposure Period	16 days
Frequency of Treatment	Daily, 5 days/week
Control Group	Corn oil (vehicle)
Post exposure observation period	No
Remarks for Test Conditions	Groups of 5 male and 5 female rats were administered 0, 100, 200, 400, 800, or 1,600 mg benzaldehyde/kg bw/d in corn oil by gavage, 5 days/week for a period of 16 days. Animals were housed 5 per cage. Water and feed were available ad libitum. Animals were observed 2X per day, weighed on days 1 and 8 and necropsied at study termination.
NOAEL(NOEL)	400 mg/kg bw/d
LOAEL(LOEL)	800 mg/kg bw/d
Toxic Response/effects by Dose Level	All high dose rats died on day 2. 2 male and 2 female rats died in the 800 mg/kg bw/d dose group. Decreased final body weights (14% in males and 11% in females) were reported in the 800 mg/kg bw/d dose group. No other compound-related effects were reported.
Appropriate statistical evaluations?	Yes. Methodology of Kaplan and Meier (1958), Cox (1972), and Tarone (1975).
Conclusion Remarks	Based on increased mortality, the NOEL was determined to be 400 mg/kg bw/day.
Data Qualities Reliabilities	Reliability code 1. Reliable without restrictions.
Remarks for Data Reliability	NTP study
References	National Toxicology Program (1990) Toxicology and carcinogenesis studies of benzaldehyde (CAS No. 100-52-7) in F344/N rats and B6C3F1 mice. Technical Report Series 378.

Substance Name	Methyl 4-formylbenzoate
CAS No.	001571-08-0
Remarks for Test Substance	Data are for structurally related substance benzaldehyde
Method/guideline	16-day gavage study
GLP	Yes
Year	1990
Species/strain	Mouse/B6C3F1

Sex	Male and Female
Route of Administration	Gavage
Doses/concentration Levels	0, 200, 400, 800, 1,600, or 3,200 mg/kg bw/d
Exposure Period	16 days
Frequency of Treatment	Daily, 5 days/week
Control Group	Yes-vehicle
Post exposure observation period	No
Remarks for Test Conditions	Groups of 5 male and 5 female mice were administered 0, 200, 400, 800, 1,600, or 3,200 mg benzaldehyde/kg bw/d in corn oil by gavage, 5 days/week for a period of 16 days. Animals were housed 5 per cage. Water and feed were available ad libitum. Animals were observed 2X per day, weighed on days 1 and 8 and necropsed at study termination.
NOAEL(NOEL)	400 mg/kg bw/d
LOAEL(LOEL)	800 mg/kg bw/d
Toxic Response/effects by Dose Level	All mice in the 2 highest dose groups died by day 3. One male receiving 800 mg/kg bw/d died on day 10. No other compound related effects were reported.
Appropriate statistical evaluations?	Yes. Methodology of Kaplan and Meier (1958), Cox (1972), and Tarone (1975).
Conclusion Remarks	Based on increased mortality, the NOEL was determined to be 400 mg/kg bw/day.
Data Qualities Reliabilities	Reliability code 1. Reliable without restrictions.
Remarks for Data Reliability	NTP study
References	National Toxicology Program (1990) Toxicology and carcinogenesis studies of benzaldehyde (CAS No. 100-52-7) in F344/N rats and B6C3F1 mice. Technical Report Series 378.

Substance Name	Methyl 4-formylbenzoate
CAS No.	001571-08-0
Remarks for Test Substance	Data are for structurally related substance benzaldehyde
Method/guideline	13-week gavage study
GLP	Yes
Year	1990
Species/strain	Rat/F344/N
Sex	Male and Female

Route of Administration	Gavage
Doses/concentration Levels	0, 50, 100, 200, 400, or 800 mg/kg bw/d
Exposure Period	13 weeks
Frequency of Treatment	Daily, 5 days/week
Control Group	Corn oil (vehicle)
Post exposure observation period	No
Remarks for Test Conditions	Groups of 10 male and 10 female rats were administered 0, 50, 100, 200, 400, or 800 mg benzaldehyde/kg bw/d in corn oil by gavage, 5 days/week for a period of 13 weeks. Animals were housed 5 per cage. Water and feed were available ad libitum. Animals were observed 2X per day, weighed on day 0, once per week and at termination. All animals were necropsied at study termination and complete histopathologic examinations were conducted on controls, and 2 highest dose groups.
NOAEL(NOEL)	400 mg/kg bw/d
LOAEL(LOEL)	800 mg/kg bw/d
Toxic Response/effects by Dose Level	At the highest dose, final mean body weight of male rats was 26% lower than controls and 6/10 males and 3/10 females died before the study ended. In addition, multiple histopathological effects were reported including: degeneration and necrosis of the cerebellum, necrosis of the neurons in the hippocampus, hyperplasia and/or hyperkeratosis of the forestomach (with mild to moderate thickening of the squamous epithelium, degeneration of the liver, necrosis of the liver (males only), and degeneration or necrosis of the tubular epithelium in the kidney. No other compound-related effects were reported. One female rat in the 400 mg/kg bw/day group and one female control rat died.
Appropriate statistical evaluations?	Yes. Methodology of Kaplan and Meier (1958), Cox (1972), Mantel -Haenszel (1959), and Tarone (1975). The Fisher exact/Cochran-Armitage trend analysis was also used.)
Conclusion Remarks	Based on the various lesions reported at 800 mg/kg bw/d, but not at 400 mg/kg bw/d, doses selected for the 2-yr study were 200 and 400 mg/kg bw/d.
Data Qualities Reliabilities	Reliability code 1. Reliable without restrictions.
Remarks for Data Reliability	NTP study
References	National Toxicology Program (1990) Toxicology and carcinogenesis studies of benzaldehyde (CAS No. 100-52-7) in F344/N rats and B6C3F1 mice. Technical Report Series 378.

Substance Name	Methyl 4-formylbenzoate
CAS No.	001571-08-0

Remarks for Test Substance	Data are for structurally related substance benzaldehyde
Method/guideline	13-week gavage study
GLP	Yes
Year	1990
Species/strain	Mouse/B6C3F1
Sex	Male and Female
Route of Administration	Gavage
Doses/concentration Levels	0, 75, 150, 300, 600, or1,200 mg/kg bw/d
Exposure Period	13 weeks
Frequency of Treatment	Daily, 5 days/week
Control Group	Yes-vehicle
Post exposure observation period	No
Remarks for Test Conditions	Groups of 10 male and 10 female mice were administered0, 75, 150, 300, 600, or 1,200 mg benzaldehyde/kg bw/d in corn oil by gavage, 5 days/week for a period of 13 weeks. Animals were housed 5 per cage. Water and feed were available ad libitum. Animals were observed 2X per day, weighed on day 0, once per week, and at the end of the study. All animals were necropsied at study termination and complete histopathologic examinations were conducted on controls, and 2 highest dose groups.
NOAEL(NOEL)	300 mg/kg bw/d
LOAEL(LOEL)	600 mg/kg bw/d
Toxic Response/effects by Dose Level	At the highest dose, 9/10 males and 1/10 females died. At 600 mg/kg bw/d, the final mean body weight of males was 9% lower than controls. Mild to moderate renal tubule degeneration occurred in all males in the high-dose group and in 1/10 males in the 600 mg/kg bw/d group. No other compound related effects were reported.
Appropriate statistical evaluations?	Yes. Methodology of Kaplan and Meier (1958), Cox (1972), Mantel -Haenszel (1959), and Tarone (1975). The Fisher exact/Cochran-Armitage trend analysis was also used.
Conclusion Remarks	Based on the mild renal lesions and depressed body weight gain, the doses selected for the 2-yr study were 300 and 600 mg/kg bw/d.
Data Qualities Reliabilities	Reliability code 1. Reliable without restrictions.
Remarks for Data Reliability	NTP study
References	National Toxicology Program (1990) Toxicology and carcinogenesis studies of benzaldehyde (CAS No. 100-52-7) in F344/N rats and B6C3F1 mice. Technical Report Series 378.

Substance Name	Methyl 4-formylbenzoate
CAS No.	001571-08-0
Remarks for Test Substance	Data are for structurally related substance benzaldehyde
Method/guideline	Carcinogenicity assay
GLP	Yes
Year	1990
Species/strain	Rat/F344/N
Sex	Male and Female
Route of Administration	Gavage
Doses/concentration Levels	0, 200, or 400 mg/kg bw/d
Exposure Period	Up to 104 weeks
Frequency of Treatment	Daily, 5 days/week
Control Group	Corn oil (vehicle)
Post exposure observation period	No
Remarks for Test Conditions	Groups of 50 male and 50 female rats were administered 0, 200, or 400 mg benzaldehyde/kg bw/d in corn oil by gavage, 5 days/week for a period of 2 years. Animals were housed 5 per cage. Water and feed were available ad libitum. Animals were observed 2X per day, weighed on day 0, once per week for the first 13 weeks, once per month for the remainder of the study and at termination. All animals were necropsied at study termination and complete histopathologic examinations were conducted on controls, highest dose group, and on low-dose animals dying before study end.
NOAEL(NOEL)	200 mg/kg bw/d
LOAEL(LOEL)	400 mg/kg bw/d
Toxic Response/effects by Dose Level	There was no effect on body weights. Survival was significantly decreased in the high-dose male group after day 373. No other effect on survival was reported. In high-dose males, hyperlasia and adenomas of the exocrine pancreas were marginally increased but the incidence of adenomas was within the range of historical corn oil vehicle controls. There was a marginal increase in the incidence of malignant mesoteliomas of the tunica vaginalis and/or peritoneum in treated male rats; however, since there was no significant increase in high-dose males relative to historical controls, the malignant mesotheliomas were not considered related to benzaldehyde treatment. There was a positive trend for mononuclear cell leukemia in male rats thought to be due to an increase in stage 1 leukemia. The slight increases in mononuclear cell leukemia reported were not considered to be related to benzaldehyde

	reported were not considered to be related to benzaldehyde treatment. In 2 females at the highest dose, squamous papillomas were reported but due to lack of accompanying hyperplasia and comparability with historical control incidences, these were not considered treatment related.
Appropriate statistical evaluations?	Yes. Methodology of Kaplan and Meier (1958), Cox (1972), Mantel -Haenszel (1959), and Tarone (1975). The Fisher exact/Cochran-Armitage trend analysis was also used.
Conclusion Remarks	Under the conditions of the 2-yr gavage study, there was no evidence of carcinogenic activity of benzaldehyde for male or female F344/N rats receiving 200 or 400 mg/kg bw/d.
Data Qualities Reliabilities	Reliability code 1. Reliable without restrictions.
Remarks for Data Reliability	NTP study
References	National Toxicology Program (1990) Toxicology and carcinogenesis studies of benzaldehyde (CAS No. 100-52-7) in F344/N rats and B6C3F1 mice. Technical Report Series 378.

Substance Name	Methyl 4-formylbenzoate
CAS No.	001571-08-0
Remarks for Test Substance	Data are for structurally related substance benzaldehyde
GLP	Yes
Year	1990
Species/strain	Mouse/B6C3F1
Sex	Male and Female
Route of Administration	Gavage
Doses/concentration Levels	0, 300, or 600 mg/kg bw/d
Exposure Period	103 weeks
Frequency of Treatment	Daily 5 days/week
Control Group	Corn oil (vehicle)
Post exposure observation period	No
Remarks for Test Conditions	Groups of 50 male and 50 female mice were administered 0, 300, or 600 mg benzaldehyde/kg bw/d in corn oil by gavage, 5 days/week for a period of 103 weeks. Animals were housed 5 per cage. Water and feed were available ad libitum. Animals were observed 2X per day, weighed on day 0, once per week for the first 13 weeks, once per month for the remainder of the study and at termination. All animals were necropsied at study termination and complete histopathologic examinations were conducted on controls, highest dose group, and on low-dose animals dying before study end.

	animals dying before study end.
Toxic Response/effects by Dose Level	There was no effect on body weight gain or survival. Focal hyperplasia characterized by increased thickness of the stratified squamous epithelium and squamous cell papillomas of the forestomach (male: control 1/50; low dose, 2/50; high dose, 5/50; female: control, 0/50; low dose, 5/50; high dose 6/50) were increased in treated animals.
Appropriate statistical evaluations?	Yes. Methodology of Kaplan and Meier (1958), Cox (1972), Mantel -Haenszel (1959), and Tarone (1975). The Fisher exact/Cochran-Armitage trend analysis was also used.
Conclusion Remarks	Under the condiitions of the 2-yr gavage study, there was some evidence fo carcinogenic activity of benzaldehyde for male or female B6C3F1 mice, as indicated by increased incidences of squamous cell papillomas and hyperplasia of the forestomach.
Data Qualities Reliabilities	Reliability code 1. Reliable without restrictions.
Remarks for Data Reliability	NTP study
References	National Toxicology Program (1990) Toxicology and carcinogenesis studies of benzaldehyde (CAS No. 100-52-7) in F344/N rats and B6C3F1 mice. Technical Report Series 378.

4.4 Reproductive Toxicity

Substance Name	Methyl 4-formylbenzoate
CAS No.	001571-08-0
Remarks for Substance	Data are for structurally related substance terephthalic acid
Test Type	Oral
GLP	Yes
Year	1982
Species/Strain	Rat/CD and Wistar
Sex	Male and Female
Route of Administration	Oral
Duration of Test	Approximately 160 days

Doses/Concentration	0.03, 0.125, 0.5, 2.0, and 5.0%
Premating Exposure period for males	Paternal: 90 days prior to and throughout mating Maternal: 90 days prior to mating, throughout mating, gestation, and lactation Offspring: 51 days; from birth through lactation and 30 days post weaning
Control Group and Treatment	Yes; concurrent no treatment
Frequency of Treatment	Daily in feed
Remarks for Test Conditions	The approximated mg/kg doses based on average feed consumption and body weight during the 90 day pre-mating period were: CD(M): 14, 59, 240, 930, 2499 CD(F): 17, 67, 282, 1107, 2783 Wistar(M): 14, 61, 249, 960, 2480 Wistar(F): 19, 78, 307, 1219, 3018 This study contrasted the toxicity of TPA in two different strains of rats. Experimental conditions were identical for both. Rats 15-17 weeks of age (n=30) were grouped housed 3/cage for the first 90 days of exposure. Body weight and feed intake were determined weekly during this time period. On Day 91, breeding pairs (n=10/sex) were housed together for 2 weeks prior to being separated. On Day 0 (delivery) the number and viability of offspring were evaluated and grossly examined. Offspring were recounted, sexed, and weighed on Day 1. These measurements were repeated at weaning on Day 21. After weaning the litters were reduced to 2/sex/dose from each of 5 litters (20 pups/dose/strain) and maintained on test diets for 30 more days (Day 51) prior to sacrifice. There were only 9 pairs of CD strain rats at the 5% diet level. Remaining animals were necropsied within a few days post weaning. At termination offspring were grossly examined and necropsied. Parental and F1 generation animals were observed 2x/day for clinical signs. Body weight gain and standard reproductive indices were assessed and statistically compared using ANOVA and Dunnett's-t-test using SAS statistical programs. Parameters evaluated consisted of: fertility index, number of offspring born per dam; number and proportion of each sex born; number (Day 0, 1, and 21) and proportion (Day 1 and 21) of each sex alive; average weight at Day 1 and 21 of all offspring and of each sex.
NOAEL(NOEL)	0.5% (CD; Wistar: 2.0%) parental – greater than 5.0% (CD and Wistar) reproductive
Remarks for Results	Parental Effects: Following 90 days of exposure to TPA, statistically significant decreases in food consumption were observed in CD females treated with 2% and 5%, and in both sexes of Wistars treated with 5%.

Body weights were statistically decreased after 13 weeks in both sexes of CD rats on 2% and 5% TPA diets, and in males exposed to 0.03%. This effect occurred in Wistars (both sexes) only at the 5% level. There were 5 deaths (3 CD females, 1 Wistar/sex) reported during weeks 4-13 in animals given 5% TPA in the diet.

During the one-generation component of the study 3 CD (1 male at 2.0%, 1/sex at 5.0%) and 4 Wistar female (2 at 5.0% and 2 at 0.03%) rats died.

There was no effect of treatment on fertility index and litter size.

Offspring Effects: There were no effects of treatment on litter size, sex ratio, or total number of offspring. While no control offspring were found dead on Day 0, 17 Wistar pups (1 at 0.03%, 2 at 0.125%, 1 at 0.5%, 12 at 2.0% (2 from one dam and 10 from another)) and 23 CD pups (1 at 0.5%, 7 at 2.0% (3 dams) and 15 at 5.0% (3 dams; with 11 from one of them)) were found dead. No statistical differences were noted in viability on Days 0, 1, or 21 in either strain. In CD rats, survivability on Day 21 was reduced in both sexes of offspring whose parents had been exposed to 5% TPA in the diet.

In Wistar rats, body weights of both sexes of offspring from dams given 5.0% were reduced at Day 1. On Day 21, body weight was reduced in both strains of offspring from dams that ingested 5% TPA in the diet. Increased postnatal deaths on Day 1 and decreased survivability to Day 21 were noted in the 2% and 5% groups. At these dose levels, several large litters of pups were lost to dams suffering obvious signs of toxicity. Several of these dams did not allow the pups to nurse or attend to the litters. These pups were noted not to have milk in their stomachs and presented clinically as being very weak. These dams were consuming dietary levels of TPA known to cause reduced feed consumption, diarrhea and gastric trichobezoars (hairballs) and induce the formation of renal and bladder calculi. Unscheduled deaths during the postweaning period (Day 21-51) were confined to the 5% TPA group (18 Wistar and 16 CD) and were associated with a very high incidence of renal and bladder calculi. Renal and bladder calculi were noted in all animals exposed to 5% that were necropsied at Day 21. Day 51 necropsy findings also reported a very high incidence of renal and bladder calculi and the histological sequelae of the presence of the calculi.

Other studies have demonstrated an increased incidence of renal and bladder calculi formation in weanling animals when compared to adults consuming the same dietary level of TPA. This apparent increased sensitivity can be explained by the large amount of feed consumed in relation to body weight for young animals experiencing their initial growth spurt. Weanling animals are not more sensitive to TPA when the results are expressed on a mg/kg basis.

Offspring toxicity F1 and F2 0.5% (CD and Wistar)

Conclusion remarks The NOAEL for reproductive toxicity was greater than 5% in the diet (approximately 2480-3018 mg/kg/day). Whereas, the

	diet (approximately 2480-3018 mg/kg/day). Whereas, the NOAEL for parental toxicity and the F1 generation was 0.5% TPA in the diet (approximately 240-307 mg/kg/day).
Data Reliabilities Qualities	Reliability code 1. Reliable without restriction.
Remarks for Data Reliability	Code 1. Comparable to guideline study.
References	Chemical Industry Institute of Technology (CIIT) (1982) A Ninety-Day Study of Terephthalic Acid (CAS No. 100-21-0) Induced Urolithiasis and Reproduction Performance in Wistar and CD Rats. CITI Docket 11622.

Substance Name	Methyl 4-formylbenzoate
CAS No.	001571-08-0
Remarks for Substance	Data are for structurally related substance dimethyl terephthalate
Test Type	Oral
Year	1973
Species/Strain	Rat/Long-Evans Hooded
Sex	Male and Female
Route of Administration	Oral-Diet
Duration of Test	Through weaning of F1 animals
Doses/Concentration	0.25, 0.50, or 1.0%
Premating Exposure period for males	Males 115 days prior to mating throughout gestation, parturition and lactation
Premating Exposure period for females	Females 6 days prior to mating throughout gestation, parturition and lactation
Frequency of Treatment	7-Days/week (diet)
Remarks for Test Conditions	Males were fed DMT diets for 115-days. These males were then mated with virgin females that had been on test diets for 6 days. After mating, the pregnant females were fed the DMT diets throughout gestation, parturition and lactation
NOAEL(NOEL)	1.0% parental
Offspring toxicity F1 and F2	0.25%
Remarks for Results	No signs of toxicity were observed in either the male or female parental animals (P). No effects were observed on fertility, reproductive capacity, libido, pregnancy, gestation, litter size, or offspring viability due to consumption of DMT. Pups born to parents fed 0.5 and 1.0% DMT had significantly lower average body weights at weaning when compared to the controls
Data Reliabilities Qualities	Reliability code 2. Reliable with restriction.

Remarks for Data Reliability	Code 2. Basic data given: comparable to guidelines/standards.
References	Krasavage, W.J., Yanno, F.J., and Terhaar, C.J. (1973) Dimethyl terephthalate (DMT): Acute Toxicity, Subacute Feeding and Inhalation Studies in Male Rats." J. Amer. Ind. Hyg. Assoc., 34(10):455-462.

Substance Name	Methyl 4-formylbenzoate
CAS No.	001571-08-0
Remarks for Substance	Data are for structurally related substance benzaldehyde
Method/Guideline	Reproductive toxicity
Test Type	1-generation
GLP	No
Year	1967
Species/Strain	Rat/white
Sex	Male and Female
Route of Administration	Gavage
Duration of Test	32 weeks
Doses/Concentration	2 mg/rat, every other day (approximately 5 mg/kg bw/d)
Premating Exposure period for males	Not described
Premating Exposure period for females	Not described
Control Group and Treatment	Ten control animals received only the vehicle oil.
Frequency of Treatment	Every other day
Remarks for Test Conditions	Two mg benzaldehyde was administered by gavage to 10 breeding age rats every other day (approximately 5 mg/kg bw/d) for a period of 32 weeks. Ten control animals received only the vehicle oil. Two pregnancies per rat were studied, one at 75 days and one at 180 days. The parameters examined included the number of pregnant females, number of offspring born, pup body weights at days 7 and 21 postpartum, and pup vitality.
Appropriate statistical evaluations	Not described
Remarks for Results	There was no statistical significant difference between treatment and control groups. It was reported that fewer females in the treated group became pregnant; however, no data or statistical analyses were performed, and the authors concluded that treatment did not cause a significant change in any of the parameters measured.

	any of the parameters measured.
Actual dose received by dose level and sex	Approximately 5 mg/kg bw/d
Parental data and F1 as Appropriate	Fewer treated females became pregnant; however, significance could not be determined.
Offspring toxicity F1 and F2	No effects reported.
Conclusion remarks	It was concluded that treatment did not affect reproduction.
Data Reliabilities Qualities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Code 4.Only secondary literature (review, tables, books, etc.).
References	Sporn A., Dinu, I., and Stanclu, V. (1967) Cercetari cu privire la toxicitatea aldehidei benzoice. [Research regarding the toxicity of benzaldehyde.] Igiena, 16(1), 23.

4.5 Developmental Toxicity

Substance Name	Methyl 4-formylbenzoate
CAS No.	001571-08-0
Remarks for Substance	Data are for the structurally related substance terephthalic acid
Test Type	Teratology
GLP	Yes
Year	1989
Species/strain	Rat/Sprague-Dawley
Sex	Female
Route of Administration	Inhalation
Duration of Test	20 days
Doses/concentration Levels	1.0, 5.0, and 10.0 mg/m3
Exposure Period	6 hours/day on days 6-15 of gestation
Frequency of Treatment	Daily

Control Group and Treatment	Yes, control group exposed to filtered room air
Remarks for Test Conditions	Female rats weighing 117-150 g were quarantined and housed 2/cage with 1 male. Confirmation of mating was via evidence of sperm in a vaginal smear (Day 0), after which females were housed singly. The study consisted of 26-27 timed-pregnant dams per dose level. Exposures were by whole body inhalation conducted in 2 m3 chambers with an airflow rate of 305-420 l/min. Test article was ground to respirable-sized particles using a Retsch Ultra-Centrifugal Mill. Chambers were sampled 2x/exposure period and TPA levels were determined by spectrophotometric analysis. Particle size was determined using a cascade impactor. Temperature, humidity and airflow were measured hourly. Animals were observed twice daily and given detailed physical exams daily on days 0 and 6-20. Dams were weighed on Days 0, 5 (randomization into groups), 6 (exposure initiation), 11, 16, and 20 (study termination). Standard "guideline" postmortem procedures were carried out on the females and their fetuses. Data were analyzed in an appropriate statistical manner using log transformations, multivariate ANOVA, single factor ANOVA and Dunnett's-"t"-test depending on the nature and type of end-point assessed. The dam was considered to be a random factor and the pup a nested factor within the dam.
NOAEL(NOEL) maternal toxicity	Greater than 10.0 mg/m3
NOAEL (NOEL) developmental toxicity	Greater than 10.0 mg/m3
Maternal data with dose level	No mortalities occurred in any group. The incidences of clinical signs observed in rats exposed to TPA were similar to controls. No statistically significant differences were noted in mean dam body weight or weight gain, uterine weight, or implant number.
Fetal Data with Dose Level	No statistically significant differences were noted in mean litter weights, pup viability, or number of fetal malformations. External soft tissue examinations did not indicate any differences from control. However, internal examinations showed a slight increase in the incidence of rib anomalies in the middle dose (5.0 mg/m3) group. This was only significant when all the various types of rib anomalies were added together.
Appropriate statistical evaluations	Yes
Remarks for Results	Rib anomalies were not deemed to be an indicator of teratogenesis because they were common variations, were not elevated in a dose-related manner, and occurred at a rate that was within the range of the laboratories own historical controls. Furthermore, no other signs of embryotoxicity were associated with this change
Conclusion remarks	There was no evidence of maternal or developmental toxicity at atmospheric concentrations up and including 10.0 mg/m3
Data Qualities Reliabilities	Reliability code 2. Reliable with restrictions.

Remarks for Data Reliability	Code 2. Basic data given: comparable to guidelines/standards.
References	Amoco Corporation (1989b) A Segment II Inhalation Teratology Study of Terephthalic Acid in Rats. Conducted by IIT Research Institute. IITRI Study #1448.

Substance Name	Methyl 4-formylbenzoate
CAS No.	001571-08-0
Remarks for Substance	Data are for in vivo metabolite terephthalic acid
Method/Guideline	Postnatal mouse screening test (Chernoff and Kavlock, 1982; Waters, 1983)
Test Type	Developmental
GLP	Yes
Year	1986
Species/strain	Mouse/CD-1
Sex	Female
Route of Administration	Gavage
Duration of Test	Up to day 3 postpartum
Doses/concentration Levels	0 or 550 mg/kg bw/d in corn oil
Exposure Period	Gestation days 6-15
Frequency of Treatment	Daily
Control Group and Treatment	The control group received corn oil only.
Remarks for Test Conditions	In a preliminary dose range-finding study, groups of 4 CD-1 mice were administered 200, 380, 720, 1,370, or 2,605 mg benzyl alcohol/kg bw/d by gavage during gestation days 6-15. No control group was used. All animals died at the highest dose and 2 animals died at the second highest dose. At 720 mg/kg bw/d, there was no signs of toxicity except for reduced
NOAEL(NOEL) maternal toxicity	Greater than 550 mg/kg bw/d
NOAEL (NOEL) developmental toxicity	Greater than 550 mg/kg bw/d
Maternal data with dose level	All parameters tested, including average number of live pups/litter, postnatal survival, and pup body weight, were statistically similar for the treated and control animals.
Fetal Data with Dose Level	All parameters tested, including gestation index were statistically similar for the treated and control animals.
Appropriate statistical evaluations	Yes. Results were analyzed by Bartlett's test, F-test, ANOVA, Fischer's exact test, Mann-Whitney U-Test

Conclusion remarks	In this assay, benzyl alcohol did not produce evidence of developmental toxicity.
Data Qualities Reliabilities	Reliability code 1. Reliable without restriction.
Remarks for Data Reliability	Audited study conducted under GLP.
References	York R.G., Barnwell, P. and Bailes, W. (1986) Final Report. Screening of Priority Chemicals for Reproductive Hazards. Environmental Health Research & Testing, Inc. No. ETOX-85-1002.

Substance Name	Methyl 4-formylbenzoate
CAS No.	001571-08-0
Remarks for Substance	Data are for structurally related substance dimethyl terephthalate
Species/strain	Rat/Wistar
Sex	Female
Route of Administration	Oral-Gavage
Doses/concentration Levels	1000 mg/kg
Exposure Period	Gestation days 7-16
Frequency of Treatment	Single daily exposure
Control Group and Treatment	Yes, concurrent no treatment
NOAEL(NOEL) maternal toxicity	Greater than 1000 mg/kg
NOAEL (NOEL) developmental toxicity	Greater than 1000 mg/kg
Remarks for Results	Animals were sacrificed on Day 21. No abnormal developmental effects and no pre- or post-implantation losses were noted. No maternal effects were noted.
Data Qualities Reliabilities	Reliability code 3. Not reliable.
Remarks for Data Reliability	Code 3. Documentation insufficient for assessment.
References	Hoechst AG (1986). Dimethyl terephthalate, investigation of embryotoxic action in Wistar rats on oral administration. Unpublished report No. 86.0859. Commissioned by the Employment Accident Insurance Fund of the Chemical industry. Dimethyl terephthalate, BG Chemie Toxicological Evaluations 1 Potential Health Hazards of Existing Chemicals, Springer-Verlag, Berlin Heidelberg New York London Paris Tokyo Hong Kong Barcelona.

Substance Name	Methyl 4-formylbenzoate
CAS No.	001571-08-0
Remarks for Substance	Data are for structurally related substance benzaldehyde
Method/Guideline	Postnatal mouse screening test (Chernoff and Kavlock, 1982)
Test Type	Developmental
GLP	Yes
Year	1983
Species/strain	Mouse/CD-1
Sex	Female
Route of Administration	Gavage
Duration of Test	Up to day 3 postpartum
Doses/concentration Levels	750 mg/kg bw/d
Exposure Period	Gestation days 6-13
Frequency of Treatment	Daily
Control Group and Treatment	A control group of 50 mice gavaged with distilled water only.
Remarks for Test Conditions	750 mg benzyl alcohol/kg bw/day was administered by gavage to 50 mice on gestation days 6-13. A control group of 50 animals were given distilled water only. Maternal body weight gain and mortality, mating, gestation, numbers of live and dead pups per litter, total litter weight on days 1 and 2 postpartum, litter weight change between days 1 and 3 postpartum, and pup survival on days 1 and 3 postpartum were recorded. Clinical signs of maternal toxicity were reported.
Maternal data with dose level	Clinical signs of maternal toxicity included hunched posture, tremors, inactivity, prostration, hypothermia, ataxia, dyspnea, swollen or cyanotic abdomen, and piloerection. There was no significant difference in maternal body weight measured on days 4 and 7 of gestation between treated and control animals. However, statistically significant decreases were observed in treated females on gestation day 18 and day 3 postpartum. Maternal body weight gain during days 7-18 of gestation was also significantly lower than that of controls. Eighteen deaths were reported during the treatment period and they were all attributed to the treatment. One more death was reported the day after treatment was terminated.
Fetal Data with Dose Level	Significant differences were also observed in pup body weight and weight gain, including mean pup weight per litter, mean litter weight change, and mean pup weight change (between day 1 and 3 postpartum). No differences were observed in the mating or gestation indices, the total number of resorptions, the number of live pups per litter, or in pup survival.

Appropriate statistical evaluations	Yes. Results were analyzed by ANOVA, Kruskal-Wallis H test, and ANCOVA.
Conclusion Remarks	Although the authors concluded that benzyl alcohol was a potential reproductive hazard, the effects observed were in conjunction with significant maternal toxicity.
Data Qualities Reliabilities	Reliability code 2. Reliable with restrictions.
Remarks for Data Reliability	NIOSH study. Audited and found to follow SOPs, but not reported to be GLP.
References	Hardin B.D., Schuler R.L., Burg J.R., Booth G.M., Hazelden K.P, MacKenzie K.M., Piccirillo V.J., and Smith K.N. (1987) Evaluation of 60 chemicals in a preliminary developmental toxicity test. Teratog. Carcinog. Mutag., 7, 29-48.